Utility of fluoro-deoxy-glucose positron emission tomography (FDG-PET) to predict a pelvic lymph node involvement (LNI) in patients (pts) with muscle-invasive bladder cancer (MIBC) enrolled in neoadjuvant therapy trials.

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Background: FDG-PET is reported to have limited utility in pts with MIBC. However, standard computed tomography (CT) imaging can often underestimate disease extent, and its role in predicting a pathological pelvic lymph node involvement (LNI) is very limited. Previous findings from PURE-01 trial reported a potential use of FDG-PET to exclude the few pts with T2-4N0M0 and pelvic LN uptake from neoadjuvant trials with immune-checkpoint inhibitors (ICI; PMID: 33071107). The aim of this study was to extend these findings to a wider range of experimental therapies. **Methods:** We collected the data of pts with clinical stage T2-4N0-1M0 MIBC included in past and ongoing neoadjuvant trials sponsored by our center, including single agent or combination of immune-checkpoint inhibitors (ICI), ICI+chemotherapy (ChT), standard ChT and sacituzumab govitecan. All pts had predominant urothelial carcinoma (UC) histology and were staged with standard thorax-abdomen CT scan and with PET/CT scan during screening and after treatment, before radical cystectomy (RC). PET/CT images were evaluated qualitatively for increased or abnormal areas of FDG uptake with corresponding anatomic alterations in CT slices. All pts underwent templated pelvic lymph node dissection (LND) with packeted node submission. Multivariable logistic regression analyses (MVA) for pathological LNI prediction were run, including cT-stage and the presence of variant histologies (VH). **Results:** A total of 149 pts (298 PET scans) were identified, treated between 02/2017 and 08/2023. 112 pts (75.2%) received ICI, 26 (17.4%) ICI+ChT, 11 (7.4%) the remaining therapies. 36 pts (24%) had a VH, 72 (48%) a cT3-4 stage, and 12 (8.1%) a cN1 stage. In total, 20 (13%) and 16 (11%) pts had PET+ pre- and post-therapy, respectively. The accuracy of FDG-PET and CT scan in predicting LNI in overall pts was similar, both pre-therapy (85.3% and 86.7%) and post therapy (86.7%, 84.6%), the only exceptions being a lower accuracy of PET to predict presacral LNI (76.6%, 78.8% pre- and post-therapy) and in VH pre-therapy (84.3% vs 90.9% PET vs CT). A pre-therapy FDG uptake significantly predicted a pathological LNI in MVA (OR: 17.8, 95%CI: 4.18-94.86, $p<0.001$, AUC: 0.89), with consistent results in T2-4N0M0 cohort (OR: 18.17, 95%CI: 4.15-99.25, $p<0.001$, AUC: 0.84). **Conclusions:** Despite the proportion of FDG-PET positive pts was modest in T2-4N0-1M0 MIBC, we were able to confirm that these pts were predicted to be poor responders to neoadjuvant therapies regardless of the type of treatment. FDG-PET had lower prediction ability of LNI in presacral LN region and in pts with a VH. This information should be critically considered for patient selection in neoadjuvant therapy trials. Research Sponsor: None.

Estimating the impact of adjuvant treatment with nivolumab on long-term survivorship rates compared with surveillance: Analyses of disease-free survival (DFS) from the phase 3 CheckMate-274 trial.

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Background: Durable DFS and cure are the ultimate goals for the treatment of muscle invasive urothelial carcinoma (MIUC) with radical cystectomy. This analysis employed mixture cure models (MCMs) to estimate the underlying cure fraction among high-risk MIUC patients following radical resection in the Phase 3 CheckMate-274 study. **Methods:** MCMs were applied to patient-level DFS data from the trial (minimum follow-up: 31.6 months). Intention-to-treat (ITT) population and the subpopulation with tumor PD-L1 expression ≥1% were analyzed separately for nivolumab (NIVO) and placebo (PBO) arms. In MCMs, the patient populations were assumed to consist of two exclusive subgroups as cured and uncured. Cured subgroup was assumed to be free of disease recurrence and disease-related mortality risks. The uncured subgroup was at the risk of both disease recurrence and all-cause mortality. DFS for the cured subgroup was estimated using background mortality rates published by WHO matched to the trial's demographic characteristics. DFS for the uncured subgroup was modelled using parametric distributions, which were characterized along with the cure fraction by maximum likelihood methods. Model selection was primarily based on clinical plausibility of estimated DFS for the uncured subgroup. Visual comparison of the fits from the MCMs to the reported DFS data from the trial and goodness-of-fit statistics also assisted model selection. **Results:** In the trial, 353 patients were treated with NIVO (mean age: 65.3; male: 75.1%; PD-L1≥1%: 39.7%) and 356 patients were in PBO control (mean age: 65.9; male: 77.2%; PD-L1≥1%: 39.9%). Selected models estimated almost all uncured patients to experience recurrence within 5 years. The estimated cure fraction in the ITT population ranged from 43.1%-45.1% in the NIVO arm (95% CI: 36.7%-51.6%), and 36.4%-37.0% in the PBO arm, (95% CI: 30.9%-43.0%) for clinically plausible models. Projected range of 10-year mean DFS for the ITT patients was 4.38-4.47 years in the NIVO arm and 3.61-3.64 years in the PBO arm. Estimated cure fractions in the PD-L1≥1% subpopulation ranged from 59.1%-61.0% in the NIVO arm (95% CI: 48.9%-72.0%), and 35.9%-36.9% in the PBO arm, (95% CI: 27.5%-45.9%). Projected range of 10-year mean DFS for the PD-L1≥1% subpopulation was 5.54-5.65 years in the NIVO arm and 3.54-3.57 years in the PBO arm. **Conclusions:** In the adjuvant treatment of MIUC, relative to radical resection only, systemic therapy with NIVO is associated with a 6-9 percentage points higher cure fraction in the ITT population. Tumor PD-L1≥1% expression was associated with higher cure fractions in the NIVO arm but had only negligible impact on the underlying cure fraction in the PBO arm. Clinical trial information: NCT02632409. Research Sponsor: Bristol Myers Squibb.

Correlation of urinary comprehensive genomic profile with risk of recurrence of BCG-unresponsive non-muscle invasive bladder cancer treated with atezolizumab in SWOG S1605.

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Background: Radical cystectomy is recommended for patients with BCG-unresponsive (BU) non-muscle invasive bladder cancer (NMIBC) due to high risk of progression. Improved methods for assessing these risks would greatly facilitate the potential for bladder preservation. Here, we tested the capacity of the urinary comprehensive genomic profile (uCGP) to predict event-free survival (EFS) in patients with BU-NMIBC treated with atezolizumab in the single arm phase 2 trial SWOG S1605. **Methods:** Urine was collected from patients with BU NMIBC (CIS, Ta, T1) treated with at least one dose of intravenous atezolizumab at baseline and before the 5th cycle of therapy (3 months). The uCGP was assessed using UroAmp (Convergent Genomics). Risk scores for recurrence at baseline and at 3 months were calculated by a prespecified machine learning algorithm incorporating alterations in 60 genes and low pass whole genome sequencing, and categorized as high versus low. Molecular response was classified based on change in uCGP between the two time points. Risk scores and molecular response were submitted to SWOG for clinical correlation with EFS using a Cox model, adjusting for CIS status. Time to event was calculated from date of study entry (baseline risk) or from the 2nd collection time (3-month risk) to first high grade (HG) recurrence or persistent CIS at 3 months. Death unrelated to bladder cancer and patients last known to be alive without HG recurrence were censored at date of last visit. **Results:** Samples were provided at baseline in 89 patients and before the 5th cycle in 77; 68 had both samples available for paired analysis. The risk score at baseline was classified as high in 69% of samples (73% for CIS ±Ta/T1 and 62% for Ta/T1). At 12 and 18 months the EFS probabilities were 26% and 23% for high-risk and 67% and 51% for low-risk patients, respectively, with a HR of 2.82 (95% CI: 1.58, 5.03; $p<0.001$). The risk score at the 3-month timepoint was classified as high in 81% of samples, and the EFS probabilities at 12 and 18 months after urine collection were 26% and 22% for high-risk and 80% and 72% for low-risk patients, respectively, with a HR of 3.39 (95% CI: 1.41, 8.13; $p<0.006$). Molecular response to treatment was classified as complete (CR) in 8%, partial (PR) in 14%, stable (SD) in 25% and progression (PD) in 46%, with 7% having no detectable genomic abnormalities at both time points. Clinical recurrence was observed by 18 months in 0/6 patients with CR, 7/9 (78%) with PR, 11/14 (79%) with SD and 25/33 (76%) with PD by genomic profile. **Conclusions:** This study suggests that uCGP at baseline and after 4 cycles of treatment can identify genomic patterns associated with an increased risk of HG persistence, recurrence or progression in BU NMIBC treated with immune checkpoint inhibition. Future studies will determine if this can be used to guide early treatment intensification. Research Sponsor: NIH/NCI grants; In part by Genentech (Roche).

LBA530 **Oral Abstract Session**

Enfortumab vedotin (EV) in combination with pembrolizumab (P) versus chemotherapy in previously untreated locally advanced metastatic urothelial carcinoma (la/mUC): Subgroup analyses results from EV-302, a phase 3 global study.

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The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the February 1, 2024, issue of the *Journal of Clinical Oncology*.

LBA531 **Oral Abstract Session**

AMBASSADOR Alliance A031501: Phase III randomized adjuvant study of pembrolizumab in muscle-invasive and locally advanced urothelial carcinoma (MIUC) vs observation.

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Predicting clinical outcomes in the S1314-COXEN trial using a multimodal deep learning model integrating histopathology, cell types, and gene expression.

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Background: Accurate prediction of response to neoadjuvant chemotherapy (NAC) is essential for optimizing treatment outcomes in muscle-invasive bladder cancer (MIBC). We present a cutting-edge multimodal deep learning model aimed at predicting outcomes of NAC from accessible H & E images and molecular data. **Methods:** We designed a Graph-based Multimodal Late Fusion (GMLF) deep learning model that integrates three types of data from the S1314-COXEN clinical trial: 1) Neural embeddings from 182 whole slide images (WSIs), generated via the ResNet50 architecture. 2) Cell types based on morphology, including cancer, necrotic, immune, and stromal cells, and their spatial positions within the tumor microenvironment extracted from WSIs using the HoVer-Net framework, a multiple-branch convolutional neural network for predicting cell types. 3) Patient-level RNA expression data derived from 1,071-dimensional gene expression vectors. The dataset was randomly divided into 80% for model training, using 5-fold cross-validation (5-fold CV), and 20% for internal validation. **Results:** Our dataset included 182 WSIs of 180 patients who were randomized to receive either gemcitabine-cisplatin or dose-dense methotrexate-vinblastine-adriamycin-doxorubicin-cisplatin. Of all patients, 30.8% demonstrated a complete pathological response (pT0 after radical cystectomy). Our GMLF model achieved an AUROC of 0.7417 $\pm$ 0.1021 for predicting whether a patient showed a complete pathologic response to NAC in a 5-fold CV. Using an 80/20 training and validation split, the model yielded an AUROC of 0.7236. Interestingly, our model emphasized the contribution of spatial information collected from WSIs. For selecting the best architecture for the histology branch, the Slidegraph+ framework, a graph neural network-based model, achieved an AUROC of 0.6938 $\pm$ 0.0565, significantly outperforming patch-level models as the second-best, which achieved AUROC of 0.5572 $\pm$ 0.1793. Shapley Additive Explanation (SHAP) analysis revealed RNA expression branch as the most influential, with a mean SHAP magnitude of 0.13, followed by the neural embeddings at 0.12. SHAP-based interpretation identified the most important expressed genes impacting model predictability, including TP63. Our gene set analysis identified the most influential pathways for predicting response, which included basal differentiation and myo-fibroblast enrichment (p-value $<$ 0.05). **Conclusions:** Our interpretable GMLF model accurately predicts NAC response in patients with MIBC by integrating standard H&E images and RNA expression data. Our model interpretations not only revealed the importance of each modality but also uncovered histopathological, cellular, and molecular underpinnings of response to NAC in MIBC. These findings open the door to AI-guided development of precision therapies for MIBC. Clinical trial information: NCT02177695. Research Sponsor: NIH/NCI.

Predictive value of dynamic changes in ctDNA and baseline biomarkers with neoadjuvant atezolizumab in operable urothelial carcinoma in the ABACUS trial.

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Background: Circulating tumour DNA (ctDNA) is being explored in the neoadjuvant setting in multiple prospective trials. Dynamic changes may be a surrogate marker of pathological complete response. ABACUS was a multi-centre, single-arm phase II trial investigating two cycles of atezolizumab before cystectomy in patients with muscle-invasive urothelial cancer who were ineligible for or refused neoadjuvant cisplatin-based chemotherapy (NCT02662309). Results of primary and secondary endpoints have been previously published. Here we perform exploratory biomarker analysis using different definitions of ctDNA response and assess correlation with tissue response at time of cystectomy in the ABACUS trial. We also assess how these definitions of response correlate with baseline biomarker expression. **Methods:** Patients with baseline PDL-1, CD8, TMB and sequential ctDNA measurements (baseline and at cystectomy) were included. ctDNA analysis was performed using the Signatera assay, PD-L1 positivity was defined as ≥5% of immune cell staining, TMB was assessed using the FoundationOne CDx assay and CD8 measurement was performed via immunohistochemistry analyses. Two definitions of ctDNA response were used—ctDNA clearance and a 50% reduction (or greater) in ctDNA variant allele frequency (VAF). Results were correlated with pathological complete response (pCR) rate at time of cystectomy and relapse-free survival. **Results:** The 2-yr DFS and OS rates in ABACUS were 68% and 77%, respectively (N=95). 40 patients had sequential DNA analysis. 43% (17/40) had pathological complete response and 20% (8/40) experienced relapse. 63% (25/40) patients were ctDNA+ at baseline, with 40% (10/25) having ctDNA response of 50% VAF reduction and 8% (3/40) achieving ctDNA clearance. 30% (3/10) of patients who had VAF reduction experienced relapse and 40% (4/10) achieved pCR. All patients with ctDNA clearance achieved pCR none relapsed. There was no association between VAF reduction of 50% and tissue response (pCR) (p=0.24). Additional analysis showed no association between a ctDNA reduction of 75% (rather than 50%) and pCR (p=0.24). Baseline PDL-1, TMB and not predictive of pathological complete response (p=0.18, p=0.77, p=0.10, respectively) or ctDNA response (p=0.54, p=0.77, p=0.74) to neoadjuvant atezolizumab. There was no difference in relapse rates between ctDNA/PD-L1+ve vs ctDNA+ve/PD-L1-ve patients (16% vs 16%, respectively). **Conclusions:** ctDNA clearance is rare but appears more accurate than 50% reduction in VAF to predict response/relapse. This is relevant for ongoing neoadjuvant trials planning to use this as an endpoint. Combining immune tissue based biomarkers with ctDNA does not appear to improve biomarker accuracy. Research Sponsor: None.

Urachal (U) and non-urachal (NU) adenocarcinomas (adenoCA) of the bladder: A comparative comprehensive genomic profiling (CGP) study.

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Background: Although both U and NU bladder adenoCA share several histological similarities, they differ in site of origin and optimal treatment paradigms. They are both relatively resistant to conventional cisplatin-based chemotherapy and surgical resection is the only curative option for organ-confined stages. The purpose of this study is to investigate the differences of genomic alterations (GA) between these tumor types, with the aim of identifying potential therapy targets. **Methods:** A total of 133 U and 328 NU adenoCA were analyzed from a series of Formalin-Fixed Paraffin-Embedded tissues obtained from clinically advanced bladder tumors. Hybrid-capture-based CGP was performed to evaluate all classes of GA. Genomic ancestry and gene signatures, including the somatic-germline nature, were determined with algorithm-based analysis of sequencing data. Tumor mutational burden (TMB) was determined based on at least 0.8 Mbp of sequenced DNA, and microsatellite instability (MSI) was assessed on at least 1500 loci. All p-values were two-sided, and multiple hypothesis testing correction was performed using the Benjamini–Hochberg procedure to calculate the false discovery rate. **Results:** Sex distribution for U adenoCA was similar (M: 50.4%; F: 49.6%), whereas more men were diagnosed with NU adenoCA (M: 63.4%; F: 36.6%). Median ages were similar between the two groups (60 vs 62 years for U and NU respectively). The most frequent GA in both U and NU cohorts included *TP53* (86.5% vs 81.1%) and *KRAS* (34.6% vs 27.7%). GAs characteristic of colorectal adenocarcinoma, such as *SMAD4* and *GNAS*, were more common in U vs NU (28.6% vs 16.5% for SMAD4, p= 0,069; 18% vs 8.8% for GNAS, p= 0,071). Conversely, mutations typical of urothelial carcinoma, including *TERT* and *RB1*, were prevalent in NU adenoCA (14.7% vs 0.77% for *TERT*, $p<0.01$; 9.2% vs 2.3% for *RB*, p=0,071). Notably, both U and NU adenoCA exhibited targetable GA in *PIK3CA* (7.5% vs 7.9%) and *ERBB2* (6.8% vs 7.6%). Biomarkers associated with potential benefit from anti-PD(L)1 were infrequent. These tumors were generally MSI stable, with a low TMB (2.61 vs 3.48 mut/Mb for U and NU respectively) and did not frequently show PD-L1 expression even at a low cut-off of $> 1\%$ (5 cases in U vs 4 in NU). Genomic ancestry distributions were similar, with EUR frequency 66% in U and 68% in NU patients. Genomic signatures were similar with both tumor types featuring a predominant mix of APOBEC (25/50%) and MMR signatures (75/36%). **Conclusions:** U and NU adenoCA revealed notable differences in GA, while PIK3CA and ERBB2 were identified as potential therapy targets. Putative biomarkers of response to anti-PD(L)1 were uncommon. Limitations include lack of clinical data, tumor heterogeneity and retrospective nature. This study highlights the potential of CGP to personalize the treatment of bladder adenoCA and may inform clinical trial designs for these tumors. Research Sponsor: None.

Defining molecular features associated with microsatellite instability and response to immune checkpoint blockade in urothelial carcinoma.

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Background: Microsatellite instability (MSI) and deficient mismatch repair (dMMR) are associated with sensitivity to immune checkpoint blockade (ICB) in urothelial carcinoma (UC). MSI status may only partially explain this sensitivity, and the molecular features that distinguish MSI-high (MSI-H) UC are not well described. **Methods:** Retrospective review of UC patients having undergone targeted exome sequencing of up to 505 genes was performed. Using the previously validated MSIsensor score, we identified MSI-H (score ≥10) and MSI stable (MSS) (score <3) UC tumors. Tumor mutational burden (TMB) was quantified. Gene alterations enriched in MSI-H UC were evaluated using the false discovery method with $q<0.05$ considered statistically significant. Mutational process signatures (MPS) were characterized using COSMIC v3.3. Survival analysis was performed using the Kaplan-Meier method with Cox proportional-hazards to determine progression-free (PFS) and overall survival (OS) based on molecular features. **Results:** Targeted exome sequencing data were available for 3,811 UC specimens representing 2,608 patients, of which 471 carried a diagnosis of upper tract UC. Of the total, 60 (1.6%) MSI-H tumors from 55 (2.1%) patients were identified. Germline testing (n=52) revealed dMMR mutations in 24 cases (46.2%) with MSH2 (59.6%) being most common. Median MSIsensor score was 19.8 (IQR 15.5, 27) and median TMB was 52.7 mut/Mb (IQR 39.7, 63.2). Notable gene alterations enriched in MSI-H tumors are summarized in Table 1. Dominant MPS in MSI-H UC included dMMR (85.0%), APOBEC (8.3%), and Aging (6.7%). MSI-H tumors clustered with dMMR mutational signatures SBS6 and SBS44. A total of 21 MSI-H and 160 MSS patients having received ICB for metastatic disease were identified for survival analysis. Median follow-up was 18.4 months (IQR 6.6, 58.5). MSI-H UC demonstrated superior PFS (HR 0.34, 95% CI 0.22-0.55) and OS (HR 0.48, 95% CI 0.28-0.80) following ICB. There was no association between TMB or MPS and survival following ICB in MSI-H UC. In MSS UC, TMB ≥10 mut/mB was associated with improved PFS (HR 0.56, 95% CI 0.40-0.79) and OS (HR 0.71, 95% CI 0.50-1.0). **Conclusions:** Targeted sequencing reveals distinct genomic features of MSI-H UC. The findings from this relatively large clinical cohort of MSI-H UC patients affirm previous associations between MSI status, TMB, and response to ICB in metastatic UC. Research Sponsor: Ruth L. Kirschstein Institutional National Research Service Award (T32).

Notable somatic gene alterations enriched in MSI-H UC.

Gene	MSI-H	MSS	Log^2 Ratio	q-value
MSH2	34 (56.67%)	62 (2.31%)	4.62	1.16E-33
MSH6	17 (28.33%)	73 (2.72%)	3.38	3.69E-11
MLH1	16 (26.67%)	49 (1.82%)	3.87	2.77E-12
PMS2	2 (3.33%)	58 (2.16%)	0.63	0.642
FGFR3	35 (58.33%)	675 (25.12%)	1.22	9.85E-07
ERBB2	22 (36.67%)	476 (17.71%)	1.05	2.45E-03
ARID1A	46 (76.67%)	706 (26.27%)	1.54	5.21E-14
KMT2D	59 (98.33%)	695 (25.87%)	1.93	1.95E-30
CREBBP	48 (80.00%)	376 (13.99%)	2.52	5.47E-27

Outcomes in patients (pts) with advanced urothelial carcinoma (aUC) treated with enfortumab vedotin (EV) after switch maintenance avelumab (MAv) in the UNITE study.

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Background: MAv is approved in pts with aUC without progression (PD) on 1L platinum-based therapy (PBT). As pts in the pivotal EV trials had not received MAv after PBT, data on outcomes with EV post-MAv are limited. We examined outcomes with EV post-MAv in the multicenter retrospective UNITE study. We hypothesized that outcomes would be similar to published EV data. **Methods:** Pts who received sequential PBT, MAv, then EV monotherapy were included. Investigator-assessed observed response rate (ORR) was assessed for evaluable pts with scans after $\geq$ 1 cycle EV using χ^2 test and logistic regression. Progression-free and overall survival (PFS, OS) were measured from EV start and assessed using KM method and Cox proportional hazards model. **Results:** Among 633 pts at 16 US sites, 49 received PBT and MAv then EV. Median age 72; 63% men; 96% Caucasian; 82% ECOG PS 0/1, 71% lower tract tumor; 65% pure urothelial histology; 71% visceral or bone mets; 33% Bellmunt score (BS) 2-3. In terms of PBT, 67% had cisplatin-based (cis); 26% carboplatin-based (carbo); 6% both cis- and carbo-based therapy. Best response to PBT was CR/PR/SD for 12% / 59% / 29% pts, respectively. Median time from PBT start to EV start was 8.5 months (mo) (3.9-21.2). Median follow up from EV start was 8.5 mo (95%CI 6.7-15.0). ORR to EV was 54%; median PFS and OS were 7.0 mo (95%CI 5.8-13.3) and 13.3 mo (95%CI 10.8-NR). Median PFS2 measured from PBT start until PD after starting EV or death was 17.5 mo (95%CI 15.2-22.5). Median OS from PBT start was 22.5 mo (95%CI 18.6-NR); 29% of pts remained on EV at data cutoff; 43% received subsequent therapy (Tx) after EV with median time to next therapy 6.4 mo (1.8-15.9). Outcomes did not differ among subgroups, except for improved PFS and OS in pts with BS 0-1 vs BS 2-3 (Table). **Conclusions:** Pts with aUC treated with EV after MAv had outcomes consistent with data for EV in PBT- and checkpoint inhibitor-refractory aUC. These data support the use of EV as third-line Tx after progression on MAv but should be validated in larger cohorts. Research Sponsor: None.

Subgroups	ORR to EV	mPFS: mo (95%CI)	mPFS: HR (95%CI)	mOS: mo (95%CI)	mOS: HR (95%CI)
Cis- vs Carbo-PBT (n=33 vs 13)*	50% vs 62%; OR 0.63, p=0.49	8.3 (6.0-14.3) vs 7.0 (5.3-NR), p=0.59	1.26 (0.55-2.87), p=0.59	13.3 (10.8-NR) vs NR (7.6-NR), p=0.33	1.85 (0.52-6.54), p=0.34
CR/PR vs SD on PBT (n=35 vs 14)	62% vs 33%; OR 3.27, p=0.10	10.8 (6.0-NR) vs 5.9 (2.5-NR), p=0.18	0.60 (0.28-1.29), p=0.19	14.3 (12.2-NR) vs 10.8 (10.1-NR), p=0.54	0.73 (0.28-1.96), p=0.54
Median time on MAv >3 mo vs ≤3 mo (n=22 vs 27)	63% vs 45%; OR 2.06, p=0.26	7.0 (5.3-NR) vs 8.3 (4.8-14.3), p=0.25	0.64 (0.30-1.37), p=0.25	17.2 (12.7-NR) vs 12.2 (7.6-NR), p=0.05	0.36 (0.13-1.05), p=0.06
BS 2-3 vs 0-1 (n=16 vs 27)	50% vs 62%; OR 0.62, p=0.47	5.3 (3.7-NR) vs 12.7 (6.0-NR), **p=0.03**	2.34 (1.05-5.19), **p=0.04**	10.1 (6.9-NR) vs 16.6 (12.7-NR), **p=0.02**	3.32 (1.11-9.88), **p=0.03**

*Excluded 3 pts with cis + carbo prior to MAv.

HER2 and PD-L1 immunohistochemistry (IHC) expression, and HER2 genomic alterations: Associations and clinical outcomes for advanced bladder cancer.

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Background: Bladder cancer (BC) has a relatively high rate of human epidermal growth factor receptor 2 (HER2) alterations. The association between HER2 mutation/amplification, HER2, and PD-L1 immunohistochemistry (IHC) expression and associations with clinical outcomes for advanced bladder cancer (BC) has not been studied. **Methods:** We retrospectively analyzed BC samples for PD-L1 and HER2 IHC expression and compared HER2 alterations from genomic profiling with the MSK IMPACT platform. HER2 IHC expression was defined as 0, 1+, 2+, 3+, and PD-L1 IHC was the combined tumor and immune cell PD-L1 expression score (CPS). HER2 alteration was defined as either pathogenic mutation and/or amplification. We studied pairwise associations between HER2 alteration, PD-L1, and HER2 IHC expression in all patients and their associations with progression-free survival (PFS) and overall survival (OS) for muscle-invasive bladder cancer (MIBC) pts. Association analyses were performed using the Wilcoxon rank-sum test or Fisher's exact test. Kaplan-Meier method and Cox proportional hazard models were used for time-to-event analyses. **Results:** Among 202 pts with HER2 IHC, 188 had MSK IMPACT, and 168 had PD-L1 CPS. The overall incidence of HER2 alteration was 22.3%; 48.2% had CPS ^{3}10, and HER2 IHC distribution was 0:18.8%, 1+:29.7%, 2+:33.7%, and 3+:17.8%. The CPS score was inversely associated with HER2 IHC expression ($p<0.001$). No association was noted between CPS score and HER2 alteration (p=0.735). HER2 altered tumors were strongly correlated with high-level HER2 IHC expression ($p<0.001$). However, 41% (n=14/34) of HER2 IHC 3+ samples did not have HER2 alterations, and 17% (n=7/36) of HER2 altered samples had HER2 IHC expression of 0. In patients with MIBC, HER2 alteration and HER2 IHC expression (0/1+ vs. 2+/3+) were not associated with PFS (p=0.5 and p=0.4, respectively) or OS for MIBC pts (p=0.84 and p=0.94, respectively). A higher PD-L1 CPS score (>=10 vs <10) was associated with improved PFS for MIBC pts (p=0.03). **Conclusions:** Our study is the first to describe an inverse correlation between HER2 IHC expression and PD-L1 CPS score. Furthermore, HER2 IHC overexpression is strongly associated with HER2 amplification, but a subset of patients with high HER2 protein expression are potentially missed by genomic profiling alone. HER2 expression by IHC or HER2 genomic alteration is not a prognostic marker for MIBC pts in this cohort. This data provides the foundation for further HER2-directed advanced BC studies. Research Sponsor: NIH; Conquer Cancer Foundation.

HER2 IHC	PD-L1 CPS<10, n(%)	PD-L1 CPS<10, n(%)	CPS total score, median (IQR)	Non-HER2 Altered, n(%)	HER2 Altered n(%)
	p-0.008		p<0.001	p-<0.001	
0	8 (9.2%)	24 (30%)	50 (14,85)	29 (20%)	7 (17%)
1+	8 (9.2%)	24 (30%)	5 (0,25)	50 (34%)	5 (12%)
2+	29 (33%)	23 (28%)	7 (1,15)	53 (36%)	10 (24%)
3+	17 (20%)	10 (12%)	4 (1,14)	14 (9.6%)	20 (48%)

IQR = Interquartile range.

Cabozantinib plus pembrolizumab as first-line therapy for cisplatin-ineligible advanced urothelial carcinoma (PemCab).

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Background: Pembrolizumab (pem) was initially approved in the first line setting for cisplatin-ineligible metastatic urothelial carcinoma (mUC) patients (pts) with high PD-L1 expression and platinum ineligible pts regardless of PD-L1 status; this later changed to only platinum ineligible pts. There is a high disease progression (PD) rate with pem monotherapy. Cabozantinib (cabo) is a multiple receptor tyrosine kinase inhibitor targeting MET and VEGFR2 approved in multiple other malignancies as monotherapy or in combination with PD-1 inhibition. We hypothesized that combination of pem and cabo therapy will be safe and efficacious in patients with treatment naïve mUC. **Methods:** This is a phase II, open label, multi-center, single arm trial evaluating the tolerability and activity of pem 200 mg every 3 weeks and cabo 40 mg daily as first-line treatment for patients with mUC. Key inclusion criteria were histologically proven locally advanced or mUC, ECOG-PS 0-2, cisplatin-ineligible (including patient refusal of cisplatin), treatment naïve, and no prior PD-1/L1 therapy. The primary endpoint was objective response rate (ORR). Key secondary endpoints included progression-free survival (PFS) and overall survival (OS). There was a lead-in safety cohort of 6 pts. We hypothesized that combination therapy would improve ORR to $>$ 32%. With 35 evaluable subjects, the lower bound of the 95% confidence interval would extend no more than 26% from the observed proportion. With $\geq$17 objective responses, the confidence interval excludes 32%. **Results:** Between December 26, 2018, and April 19, 2023, 36 pts were enrolled of which 35 were evaluable for response with the median follow up of 14.4 months (95% CI 12.2 – 16.2). The median age was 72.5y [range, 47-82]; ECOG PS 0-1 in 89% pts. Responses were observed in 15 pts (ORR= 42.8%) including complete responses in 5 pts (14.3%). Stable disease was seen in 10 pts (28.6%). The disease control rate was 68.5% (25/35). Median PFS was 7.7 months (95% CI 4.2 – 11.2). Fifty-two percent of pts developed any grade treatment-related adverse events (TRAE) attributable to either cabozantinib or pembrolizumab. The most common grade 1/2 TRAE were diarrhea, anorexia, dysgeusia, weight loss, and nausea. Forty-four percent pts developed grade 3/4 TRAEs most common being hypertension, hypophosphatemia, alanine transaminase elevation, diarrhea, and fatigue. **Conclusions:** This novel phase II trial of pem + cabo demonstrated a manageable toxicity profile and promising efficacy as first-line therapy in mUC including patient's ineligible for cisplatin. Further investigation with a focus on predictive biomarkers is ongoing. Clinical trial information: NCT03534804. Research Sponsor: Exelixis.

FGFR3 mutated (*FGFR3*mut+) urothelial carcinoma of bladder (UCB) or upper tract (UTUC): A comparative genomic landscape study.

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Background: Activating DNA sequence genomic alterations (GA) in the *FGFR3* gene including short variant (SV) mutations and kinase domain activating gene rearrangements/fusions (RE-FUS) are known drivers and relevant precision treatment targets for pts with UC. THOR trial showed a significant overall survival benefit with erdafitinib (FGFR inhibitor) vs (taxane or vinflunine) in patients (pts) with advanced UCB or UTUC. PROOF-302 trial showed higher frequency of FGFR3 GA in UTUC (30%) vs UCB (13%). We sought to explore differences in frequency of FGFR3 alterations and the genomic landscapes of *FGFR3*-altered UCB and UTUC. **Methods:** 10,402 UCB and 2,325 UTUC (combined ureter and renal pelvis) underwent hybrid capture-based comprehensive genomic profiling (CGP) using a hybrid capture-based to assess all classes of GA and measure MSI status, TMB level, genomic ancestry, genomic signature, germline mutations and HRD score. PD-L1 was determined by IHC (Dako 22C3 using the TPS system. Results were compared using the Fisher Exact method with the Benjamini-Hochberg adjustment. **Results:** *FGFR3*mut+ status was significantly more frequent in UTUC than in UBC (24.9% vs 17.7%; p<.0001) (Table). UCB pts were more often male than UTUC (P=.0003). Age (71-72 yrs), EUR ancestry (85%) and GA/tumor (8.9-9.0) were similar. The number of GA/case and the frequency of EUR ancestry were similar. Targetable GA in *ERBB2* and *PIK3CA* were more frequent in *FGFR3*mut+ UBC vs *FGFR3*mut+ UTUC. GA in *PTEN*, *TSC1* and *MTAP* currently associated with clinical trials were similar in UBC and UTUC. The KEGG ERBB and VEGF signaling pathways were more frequently identified in UCB (p=0.036) and the MMR pathway more frequently identified in UTUC (p=0.014). The HRD signature was similar in both groups (2.3-3.1%). Anti-PD(L)1 putative biomarkers included a significantly higher frequency of MSI-high status in UTUC vs UCB but no significant difference in TMB or PD-L1 expression levels. **Conclusions:** Although histologically similar, the genomic landscape of *FGFR3*mut+ UTUC has notable differences with *FGFR3*mut+ UCB. Limitations include lack of clinical data annotation. The findings may impact of clinical trial designs for UCB and UTUC, including evaluating combinations of anti-FGFR3 with other agents. Research Sponsor: None.

	UCB (10402 cases)	UTUC (2325 cases)	P-value
sex (% male)	71.2%	61.7%	0.0003
ERBB2	7.2%	4.1%	0.042
MTAP	45.9%	43.1%	NS
PIK3CA	28.8%	22.6%	0.019
TERT	79.8%	69.6%	<.0001
TP53	31.1%	27.2%	NS
MSI-high	1.8%	5.4%	<.0001
Median TMB	5.2	5	NS
PD-L1 low positive	18.0%	29.4%	NS

Demographic and prognostic factors in papillary transitional cell carcinoma: An analysis of the National Cancer Database.

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Background: Transitional cell carcinomas account for the majority of bladder cancers, with the papillary subtype comprising most of these cases. The role of race in bladder cancers has been investigated in the past, but there have been no studies that collectively investigated the role of different demographic factors in survival and mortality in papillary transitional cell carcinoma (PTCC). This study analyzes the effects of demographic factors on overall mortality (OM) in patients with PTCC. **Methods:** A retrospective cohort analysis was conducted using National Cancer Database data from 2004-2019, including 12,300 patients with histologically confirmed PTCC (ICD-O-3=8130). Sex, race (Black, White, and Other), insurance status, and median household income quartile (based on 2016-2020 American Community Survey data) were examined. Kaplan-Meier curves were used to calculate 2, 5, and 10 year survival (2-5-10 YS). Multivariable Cox regression was used to calculate hazard ratios (HR) to identify independent prognostic factors. Statistical significance was set at α=0.05. **Results:** Females had higher 2-5-10 YS and decreased OM compared to males (HR=0.85, P<.001). White patient survival was higher at 2 years compared to Black patients, but Black patient survival was higher at 5 and 10 years. There was no significant difference in OM between Black and White patients (HR=1.07, P=0.260). Patients of other races had higher 2-5-10 YS and decreased OM compared to White (HR=0.85, P=0.023) and Black patients (HR=0.80, P=0.011). Patients on Medicaid had lower 2-5-10 YS and increased OM compared to patients on private insurance (HR=1.19, P=0.036). Patients on Medicaid had higher 2-5-10 YS than patients on Medicare, but no significant difference in OM (HR=0.87, P=0.091). Patients on private insurance (HR=0.70, P<.001) and Medicare (HR=0.73, P=0.003) had decreased OM compared to uninsured patients. Patients in the fourth income quartile had decreased OM compared to patients in the first (HR=0.82, P<.001), second (HR=0.87, P<.001), and third quartiles (HR=0.90, P=0.003). **Conclusions:** Male sex, uninsured status, and lower income were associated with increased OM. Black patients and White patients had increased OM compared to patients of other races. Future research should investigate the reasons for these disparities and how to minimize them.
Research Sponsor: None.

Kaplan meier survival statistics.

Group	2 years	5 years	10 years
Male	0.726	0.522	0.333
Female	0.742	0.538	0.364
White	0.732	0.526	0.343
Black	0.728	0.537	0.361
Other Races	0.752	0.577	0.407
Private Insurance	0.804	0.644	0.510
Medicaid	0.763	0.594	0.457
Medicare	0.702	0.477	0.270

Disparities in the incidence of next-generation sequencing (NGS) among patients (pts) with advanced or metastatic prostate cancer (mPC) and urothelial carcinoma (mUC).

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Background: Based on availability of approved agents targeting tumor somatic mutations, current guidelines recommend NGS for Pts with mPC and mUC. However, large cohort studies in mPC and mUC evaluating disparities in NGS testing have not been reported. Herein, we investigated the effect of social determinant of health (SDOH) on disparities in NGS testing in a large real-world dataset of pts with mPC and mUC. **Methods:** Pts data were extracted from the nationwide Flatiron Electronic Health Record (EHR)-derived de-identified database. Inclusion: new diagnosis of advanced or metastatic (adv/met) PCa and UCa between March 2015 to December 2022 and receipt of cancer therapy (to include only treatment eligible pts). Disparities in incidence of NGS testing after adv/met diagnosis by SES, R/E, region, and insurance were assessed using Fine and Grey's (FG) modified stratified Cox proportional hazard (PH) model. FG model considered death as a competing risk. Stratification was done by year of adv/met diagnosis (accounting heterogeneity) and R/E (an effect modifier for SES, region, and insurance), assuming different baseline hazards in each stratum. All analysis done using R v.4.2.3. **Results:** Analytic cohorts comprised 11,936 pts with mPC and 6,490 pts with mUC. Hazard ratios (HR) and 95% confidence intervals (CI) from FG Cox PH models are reported in the table. For both cancer types, pts were more likely to get NGS testing when they were White, non-Hispanic (compared to Black, non-Hispanic), had higher SES, and had commercial insurance. **Conclusions:** Our data suggest an association between incidence of NGS testing and several SDOH in mPC and mUC. Further studies are needed to elucidate the reasons for these disparities and ways to mitigate them. Research Sponsor: None.

	mPC		mUC	
	HR (95% CI)	p-value	HR (95% CI)	p-value
R/E[a]				
White, non-Hispanic	ref	NA	ref	NA
Black, non-Hispanic	0.75 (0.67, 0.84)	< 0.001	0.75 (0.59, 0.96)	0.02
Hispanic	0.70 (0.60, 0.82)	< 0.001	0.93 (0.72, 1.20)	0.56
Asian, non-Hispanic	0.84 (0.63, 1.11)	0.22	0.87 (0.58, 1.29)	0.48
Others	0.97 (0.88, 1.07)	0.54	1.12 (0.98, 1.28)	0.09
SES[b]				
1 – Lowest	ref	NA	ref	NA
2	1.24 (1.09, 1.41)	0.001	1.29 (1.03, 1.61)	0.03
3	1.24 (1.09, 1.41)	0.001	1.35 (1.09, 1.65)	0.005
4	1.28 (1.13, 1.45)	< 0.001	1.31 (1.07, 1.61)	0.009
5 - Highest	1.38 (1.22, 1.57)	< 0.001	1.31 (1.06, 1.62)	0.01
Region[b]				
Midwest	ref	NA	ref	NA
Northeast	1.02 (0.89, 1.17)	0.73	1.24 (0.98, 1.57)	0.08
South	1.05 (0.94, 1.18)	0.28	1.24 (1.02, 1.51)	0.03
West	0.81 (0.70, 0.94)	0.005	1.23 (0.94, 1.61)	0.13
Insurance[b]				
Commercial	ref	NA	ref	NA
Medicare/Other government programs	0.89 (0.82, 0.98)	0.02	0.87 (0.74, 1.02)	0.09
Medicaid	0.56 (0.39, 0.80)	0.001	0.75 (0.49, 1.16)	0.20
Others	1.13 (0.98, 1.29)	0.07	1.09 (0.86, 1.37)	0.48

[a]stratified by adv/met diagnosis year. [b]stratified by adv/met diagnosis year and R/E ref: reference NA: Not applicable.

A safety net for safety net hospitals: Affiliation with cancer centers and survival outcomes in patients with metastatic genitourinary cancers.

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Background: Safety net hospitals (SNH) care for a substantial proportion of medically vulnerable populations (MVP). Addressing health disparities at a hospital level through partnerships with cancer centers is a potential strategy to improve outcomes of MVPs. We thus compared outcomes for metastatic prostate (mPCa), kidney (mKCa), and urothelial cancer (mUCC) among National Cancer Institute centers (NCI), NCI affiliated SNH (NCI-SNH), and non-affiliated SNH using the Texas Cancer Registry (TCR). **Methods:** The TCR has 98% case ascertainment of all cancers diagnosed in Texas. The TCR can identify each facility where a patient was diagnosed and treated, allowing detailed hospital level comparisons of outcomes. The TCR was queried from 2004-2017 for mPCa, mKCa, and mUCC. Publicly available data identified Texas NCIs. The top quartile of Disproportionate Share Hospital Index values identified SNH. SNH with established relationships to NCI were designated NCI-SNH and remainder were SNH. Non-SNH were hospitals not affiliated with NCI nor SNH. MVPs were defined as age $>$ 75, non-US natives, non-whites, and uninsured or Medicaid patients. Cox multivariable regression was used to assess overall mortality (OM). **Results:** Of the 1,048,464 patients in TCR, MVPs accounted for 44.7% of cases. The SNHs and NCI-SNHs accounted for 53.1% of all MVP cancer care statewide. MVPs were the majority of cases within NCI-SNH compared to other SNH or NCI (80% vs 45% vs 37.1%, $p<0.01$). TCR identified 20,503 metastatic genitourinary (GU) cancers. For mPCa, rates of hormone therapy were similar between NCI-SNH (76.7%) and NCI (76.2%), but greater than SNH (51.5%) or non-SNH (49.7%) ($p<0.01$). Receipt of chemotherapy or immunotherapy was greater at NCI-SNH compared to other SNH or non-SNH for both mKCa (36.1% vs 31.1% vs 27.1%, $p<0.01$) and mUCC (44.0% vs 36.7% vs 33.2%, $p<0.01$). On multivariable cox analysis, equivalent OM between NCI and NCI-SNH for any metastatic GU cancer (Table). OM was worse at other SNH and non-SNH compared to NCI (Table). **Conclusions:** Medically vulnerable patients made up almost half of cancer care in Texas and majority were cared for at SNH. NCI-SNHs had equivalent OM to NCI and superior OM compared to other SNH. Future initiatives to improve cancer care should focus on strengthening existing relationships between NCI and SNH, and examine mechanisms to centralize care of MVPs to these facilities. Research Sponsor: None.

MV Cox model.

Hospital Designation	HR	P-value	95% CI	
NCI*	*Ref.*	*Ref.*	*Ref.*	*Ref.*
	mPCa**			
NCI-SNH	1.01	0.86	0.88	1.17
Other SNH	1.42	$<$ 0.01	1.31	1.55
Non-SNH	1.36	$<$ 0.01	1.24	1.49
	mKCa**			
NCI-SNH	1.10	0.22	0.94	1.28
Other SNH	1.33	$<$ 0.01	1.22	1.44
Non-SNH	1.35	$<$ 0.01	1.23	1.49
	mUCC**			
NCI-SNH	0.99	0.99	0.75	1.33
Other SNH	1.38	$<$ 0.01	1.17	1.61
Non-SNH	1.23	0.02	1.03	1.47

*Reference group.
**Model adjusts for age, sex, race, nativity, insurance, region, systemic therapy, radiation.

Exploration of enfortumab vedotin (EV)–related cutaneous events by race in two real-world cohorts.

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Background: EV is an antibody drug conjugate, approved in advanced urothelial cancer (UC). The Nectin-4 target of EV is present in tumor and normal skin, and EV-related cutaneous events (EVCEs) are common. EVCEs often appear early with variable grade presentation. Continuation of EV is typically safe with supportive management, but rare life-threatening manifestations have occurred. Dermatologic conditions, including medication-related skin events are often underdiagnosed or under-staged in Black patients (pts). Black pts are also frequently under-represented in UC trials, and it is unknown whether EVCE incidence varies by skin tone. We explored whether EVCE frequency varies between Black and White pts in an urban cohort and a large community-based national dataset. **Methods:** This retrospective cohort analysis used data from Johns Hopkins Hospital (JH) and Flatiron Health (FH), a de-identified electronic health record (EHR)-derived database of community-based oncology clinics across the U.S. Pts treated with EV monotherapy at JH and in the FH database who self-identified as Black or White race were included. In the JH cohort, chart review was used to extract demographics, treatment details, and EVCEs. EVCEs were defined as any grade, new or exacerbated dermatologic event after EV initiation, not attributed to other cause. In the FH cohort, EVCEs were identified through pre-defined skin-related ICD-10 codes identified by the study authors. Odds ratios (OR) with 95% confidence intervals of EVCE incidence between Black and White pts were calculated separately for each cohort. **Results:** 78 toxicity-evaluable pts were identified in the JH cohort and 316 in the FH cohort. 12 were Black (15.4%) in the JH Cohort vs. 24 Black (7.6%) in the FH cohort. Median age was 71 years (IQR: 64-78), 20 (25.6%) were female, 50 (64.1%) pts had a primary site in the bladder, and 13 (16.7%) had EV as second-line and 49 (62.8%) as third^{-}line treatment in the JH cohort, vs. 71 years (IQR: 65-77), 84 females (26.6%), 226 (71.5%) with bladder primary site, and 122 (38.6%) and 108 (34.2%) receiving EV as second-and-third-line treatment respectively in the FH Cohort. In the JH Cohort 8 of 12 Black pts (66.7%) as compared to 32 of 58 (55.2%) White pts experienced an EVCE (Table, OR 1.63, 95% CI [0.44, 6.0]). In the FH cohort, 6/24 Black pts (25%) compared to 46 /292 White pts (15.8%) experienced an EVCE (Table, OR 1.78, 95% CI [0.67, 4.73]). **Conclusions:** In this hypothesis-generating analysis of EV treated pts, the largest reported cohort of Black EV treated pts to date, we observed an increased EVCE frequency in Black pts relative to White, though statistical significance was not demonstrated. Future prospective EV studies should aim to recruit Black patients to better characterize this finding. Research Sponsor: None.

		No EVCE	EVCE
JH Cohort (n=78)			
	White	26 (44.8)	32 (55.2)
	Black	4 (33.3)	8 (66.7)
FH Cohort (n=316)			
	White	246 (84.2)	46 (15.8)
	Black	18 (75)	6 (25)

Genomic profiling in bladder cancer across a spectrum of measured socioeconomic inequality: A retrospective review utilizing next generation sequencing.

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Background: Socioeconomic inequality (SI) is a known risk factor for worse prognosis in bladder cancer. The mechanism behind this is likely due to a complex interplay between many factors including access to care, diet and exercise disparities, and frequency of tobacco/alcohol use. There remains a scarcity of studies looking at the impact of socioeconomic inequality on tumor biology in bladder cancer, yet genomic profiling to look for biomarkers with therapeutic targetability is becoming increasingly common through testing modalities such as next-generation sequencing (NGS). This study aimed to further understanding of the effect of SI on the genomic alterations with therapeutic implications seen in bladder cancer. **Methods:** This was a retrospective analysis of 108 patients (75 male and 33 female) ranging from 18-92 years old with bladder cancer presenting to the University of Arizona Cancer Center from 2016-2023. Of these 108 patients, 97 had NGS data available. Each actionable pathogenic mutation, tissue mutational burden (TMB), and combined positive score (CPS) for PDL1 expression was recorded for each patient. TMB score of >10 and/or CPS of >10 were considered as actionable mutations for immunotherapy. The Area Deprivation Index was used to measure SI levels of each patient's neighborhood based on a national scale from 1-100 with 100 being most disadvantaged and 1 being the least. These patients were then split into three tertiles: 1-33, 34-67, and 68-100 to compare the frequency of genomic alternations using chi-squared for contingency tables and kruskal-wallis rank test for multiple samples. **Results:** Of the 97 patients with NGS, 18 were in tertile 1, 47 in tertile 2, and 34 in tertile 3. TMB-High>10 was significantly different between tertiles with the following frequencies of TMB >10: tertile 3 8/34 (23.5%), tertile 2 21/47 (44.6%), and tertile 1 10/18 (55.5%), (p=<0.05). The mean mutational burden in tertile 1, 2, and 3 was 11.3, 10.17, and 8.22 respectively (p=0.147). There was no correlation of SI with the selected frequent mutations KDM, ARID1A, TERT, TP53, PIK3CA, TP53, and TERT (p>0.05). **Conclusions:** Higher TMB in bladder cancer has been associated with a more favorable prognosis and predictive response to immunotherapy. Our results show patients from neighborhoods of higher SI have a significantly lower frequency of TMB score >10, and this could offer partial explanation for the worse prognosis seen with higher SI levels. Our relatively small sample size limits the power of our study. Further investigation through larger scale studies of the genomic alterations seen between SI levels have important implications in understanding both why and how to better address the worse outcomes seen in bladder cancers in patients with greater SI levels. Research Sponsor: None.

The association between social vulnerability and clinical trials awareness and participation: A HINTS-SEER analysis.

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Background: Clinical trials are integral to science and can ensure access to standard of care treatments, providing benefits to individual participants and society. Unfortunately, fewer than 5% of eligible cancer patients participate in clinical trials, and large facets of the population remain starkly underrepresented, excluding them from these benefits and potentially compromising the generalizability of biomedical knowledge. Adverse social determinants of health (SDOH), or social vulnerability, may affect awareness and the decision to participate in a clinical trial, especially in underrepresented or historically excluded populations. In this study, we evaluate the association between population-level SDOH and clinical trials awareness and participation. **Methods:** We performed a cross-sectional analysis of the 2021 Health Information National Trends – Surveillance, Epidemiology, and End Results (HINTS-SEER), a nationally representative survey of 1,234 cancer survivors. The primary outcomes of interest included awareness of clinical trials "as a possible treatment option for your cancer" and "participation in a clinical trial for treatment of your cancer". The primary exposure was the Centers for Disease Control and Prevention Social Vulnerability Index (CDC SVI), which was linked to each survey respondent by ZIP code of residence. Survey weighted multivariable logistic regression analyses were performed to evaluate the association between SVI quintile and clinical trial awareness and participation, adjusting for age, sex, race/ethnicity, and education level. **Results:** This survey weighted analysis represents a population of over 400,000 patients. Only 15.1% of patients were aware of clinical trials, with the most socially vulnerable patients having lower rates of awareness compared to the least socially vulnerable patients (8.5% vs. 17.9%). Similarly, only 7.7% of patients participated in a clinical trial, with the most socially vulnerable patients having lower rates of participation compared to the least socially vulnerable patients (3.0% vs. 10.1%). On multivariable analysis, the most socially vulnerable patients had significantly lower odds of clinical trials awareness (OR 0.43, CI 0.20 – 0.94) and clinical trials participation (OR 0.15, CI 0.03 – 0.73) compared to the least socially vulnerable patients, adjusting for age, sex, race/ethnicity, and education level. **Conclusions:** In this analysis of HINTS-SEER, a contemporary and novel survey of cancer survivors, rates of clinical trial awareness and participation remain concerningly low. Notably, adverse SDOH has a strong influence, with the most vulnerable patients being far less likely to be aware of or participate in a clinical trial. With the goal of achieving equitable cancer care, identifying and alleviating barriers to clinical trial participation, especially those rooted in SDOH, is critical. Research Sponsor: Bladder Cancer Advocacy Network.

Impact of insurance payer status (IS) on practice patterns and overall survival (OS) in patients (pts) with metastatic urothelial carcinoma (mUC).

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Background: Equitable access to novel therapies continues to be a significant challenge in pts with mUC. We hypothesized that insurance IS could impact practice patterns and ultimately outcomes. In this multi-institution study, we investigated the impact of IS on treatment selection and OS in pts with mUC. **Methods:** Pts diagnosed with mUC between 2010-2023 with available outcomes and insurance data were included from two NCI-designated comprehensive cancer centers. Primary IS was used to categorize pts into three groups: Medicare, private insurance, and Medicaid/uninsured. Baseline characteristics were summarized by descriptive statistics and compared via either one-way ANOVA/Kruskal-Wallis test (continuous variables), or Pearson chi-square test/Fisher's exact test (categorical variables). OS from time of diagnosis of mUC was calculated using the Kaplan-Meier method and compared amongst IS groups using log-rank test. Cox proportional hazards multivariable model was utilized to examine correlation of IS with OS. **Results:** Of the 356 pts included, 222 (62.3%) had Medicare, with 69.8% (155) having secondary coverage. Pts with private insurance or Medicaid/no insurance included 30.3% (108) and 7.3% (26) of pts respectively. As expected, pts in Medicare group had higher median age (71 yrs; range: 49-92; P<0.0001) compared to private (59; range: 31-85) or Medicaid/uninsured groups (61.0; range: 32-79) while proportion of female pts was highest in Medicaid/uninsured group (50%; P<0.0001). Race, presence of *de novo* mUC, smoking status, use of neoadjuvant chemotherapy, clinical trial participation, type and number of lines of therapy for mUC were not significantly different between the IS groups. Pts with Medicare had significantly higher OS (median: 44.8 mos; 95% CI: 35.3-58.5; p=0.001), compared to private insurance (28.4 mos; 95% CI, 24.3-39.2) and Medicaid/uninsured (29.9 mos; 95% CI, 16.8-44.4). Within the Medicare group, pts with secondary insurance in addition to Medicare had a trend towards better OS (50.6 mos; 95% CI, 25.3-49.5) compared to those without (36.2 mos; 95% CI, 25.3-49.5; p=0.06). On multivariable analysis adjusting for covariates such as age, histology, presence of visceral metastasis, and number of lines of therapy, private insurance (HR: 1.684, 95% CI: 1.184, 2.397; P=0.0038) and Medicaid/uninsured pts (HR: 1.84; 95% CI: 1.099-3.098; P=0.021) had significantly worse outcomes. **Conclusions:** Despite similar access to expertise and systemic therapy at academic centers, IS was a significant predictor of OS in pts with mUC. Pts with private insurance or Medicaid/uninsured demonstrated significantly lower OS compared to Medicare. Potential underlying drivers such as co-morbidities, access to primary care, and socioeconomic barriers could have impacted these results and warrant further examination in future studies. Research Sponsor: None.

Development of a novel RNA-based fibroblast growth factor receptor response signature (FGFR-PRS) for use in patients with urothelial cancer (UC).

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Background: Interest in FGFR-targeted (FGFRi) therapies for UC or pan-tumor use is growing (ongoing clinical studies include erdafitinib (NCT05316155; NCT04172675; NCT03390504; NCT04083976), LOXO-435 (NCT05614739), and pemigatinib (NCT03914794) following accelerated approval of erdafitinib in locally advanced/metastatic (m) post-chemotherapy UC patients with FGFR2/3 (i.e., DNA mutations and fusions) alterations (ALT). However, ALT status may not fully capture all who may show clinical benefit as responses are observed in both ALT (+) and (-) patients. Improved test strategies are needed to identify patients most likely to respond to FGFRi. FGFR-PRS is an RNA-based signature developed to capture the biology of FGFR-active tumors independent ALT status and is intended to be used as a diagnostic (Dx) to identify a broader patient population likely to respond to FGFRi. **Methods:** Known oncogenic FGFR3 ALTs (S249C, R248C, FGFR3c-Y373C, FGFR3c-G370C, FGFR3:TACC3 and FGFR3:BAIAP2L1) were used as training labels for nearest centroid classifier development as described in Dabney et al, 2005 (https://doi.org/10.1093/bioinformatics/bti681) using 2/3 of data from the TCGA BLCA dataset, predominantly comprised of muscle-invasive bladder cancer patients and a few mUC patients, for training. The resulting 80-gene signature was applied to the remaining 1/3 of TCGA and a separate BACI mUC dataset (Rose et al, 2021; https://doi.org/10.1038/s41416-021-01488-6) as test sets. In vitro drug sensitivity was evaluated using data from the Genomics of Drug Sensitivity in Cancer database (GDSC; https://www.cancerrxgene.org/). Differential gene expression (DGE) results were analyzed using WebGestalt 2019 (https://www.webgestalt.org/). **Results:** Thirteen and 18% of the TCGA and BACI UC cohorts were ALT (+), whereas 49% and 48% were FGFR-PRS (+) independent of ALT status. About half of the patients in either cohort were ALT (-)/ FGFR-PRS (-) and only 1% were ALT (+)/FGFR-PRS (-). FGFR 1-3 selective drugs had strong inverse correlations between FGFR-PRS score and IC50 across 18 GDSC bladder cancer cell lines. FGFR-PRS (+) samples had enhanced co-expression of FGFR3, FOXA1, and SHH and selected multiple differentiation ontologies. **Conclusions:** FGFR-PRS (+) captured most ALT (+) tumors and an additional 2X more with similar FGFR pathway activation. FGFR-PRS (+) tumors were associated with gene enrichments for ontologies linked to FGFR3 signaling. The correlation of FGFR-PRS score with in vitro FGFRi activity provided initial utility of the signature, which is undergoing clinical evaluation in the ALAMANCE retrospective study of UC patients treated with FGFRi or other standard-of-care therapies. Analytical validation is ongoing to support FGFR-PRS for use as a clinical trial assay and eventual Dx. Research Sponsor: GeneCentric Therapeutics, Inc.

Development of a novel RNA-based immune checkpoint inhibitor response signature (ICI-PRS) that avoids standard-of-care (SOC) prognostic signal for use in patients with urothelial cancer (UC).

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Background: Immune checkpoint inhibition (ICI) shows great promise, including approval of pembrolizumab, nivolumab and avelumab in urothelial cancer (UC). However, the overall percentage of UC patients with clinical benefit is relatively small, despite biomarker use to select patients (e.g., PD-1 expression and TMB). Recently, several accelerated approvals (atezolizumab and durvalumab) were subsequently withdrawn following failure to show improved survival compared to standard of care (SOC) treatment in Phase 3 +/- biomarker use. To address the need for better ICI biomarkers, we developed an RNA-based predictive response signature (ICI-PRS) with the primary objective of being prognostic for ICI-treated patients, but not for SOC treatment. **Methods:** A survival-based model trained on 2/3 of the combined IMVigor210 dataset (n=298 locally advanced or metastatic UC patients treated with atezolizumab) and TCGA BLCA cohort (n=405 patients treated with non-ICI SOC) identified genes associated with survival across these data sets (prognostic agnostic to therapy) and genes distinctly associated with survival with ICI treatment (candidate ICI-predictive). Candidate ICI-predictive genes were developed into a model that was applied to the remaining IMVigor210 and TCGA BLCA samples, UC-GENOME urothelial carcinoma samples, and an ICI-treated melanoma dataset (Gide et al, 2019 : DOI: 10.1016/j.ccell.2019.01.003). Associations with tumor mutation burden (TMB) were examined. Expanded models incorporating this signature with additional immune markers were also investigated. **Results:** The ICI-PRS shows consistent associations with overall survival (OS) dependent on ICI treatment status. A higher hazard ratio (HR) was found for cohorts with ICI-therapy [HR (95% CI): IMVigor test 1.23 (0.96-1.57); UCGENOME 1.35 (0.99-1.85); Gide 1.50 (1.02-2.2)]. By comparison, no association was seen in the TCGA test set in which patients received non-ICI SOC treatment (HR = 0.96 (0.73-1.3). Patients with high TMB had extended survival in both IMVigor210 and non-ICI SOC TCGA datasets (P = 0.02 and 0.001). **Conclusions:** Herein we describe the development of a novel ICI-PRS and initial demonstration that it provides ICI-treatment specific prognostic value for bladder cancer patients. ICI-PRS status was associated with extended survival in patients treated with anti-PD-L1 but not non-ICI SOC therapy. These results support the further evaluation of the ICI-PRS and potential development as a diagnostic test for selecting UC patients most likely to benefit from ICI therapy. Research Sponsor: GeneCentric Therapeutics, Inc.

Theranostic imaging and treatment of chemotherapy resistant muscle invasive bladder cancer by targeting FAP and CXCR4: The Bladder BRIDGister experience.

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Background: Patients with muscle invasive urothelial carcinoma achieving pathological complete response (pCR) upon neoadjuvant chemotherapy (NACT) have improved prognosis. Previously we did show that luminal tumors respond better to NACT (Ecke et al 2022), while the radioligand targets CXCR4 and FAP are found in chemoresistant, stroma-associated tumors. The objective of this study was to exploit the expression of CXCR4 & FAP for theranostic imaging & treatment in selected patients by radioligand instillation into the bladder to justify subsequent adopted clinical trials within the Bladder BRIDGister framework. **Methods:** FFPE tumor tissues from 511 TURB samples were prospectively collected as part of the Bladder BRIDGister. RNA was extracted by commercial kits, relative gene expression of subtyping markers and radioligand target genes were analyzed by RT-qPCR. Hierarchical clustering, Kruskal-Wallis and contingency tests were done by JMP 9.0.0 (SAS software). PET/CT Imaging by CXCR4 and/or FAP instillation was performed in selected patients followed by systemic radioligand application after completion of cisplatinum based NACT to enable improved staging. **Results:** The prospective molecular registry cohort consisted of 511 bladder cancer patients included into the Bladder BRIDGister (median age: 75, male 74% vs. female 26%) with 5% Tis, 54% Ta, 16% T1 and 15% T2 stage and concomitant CIS being in 7%. CXCR4 expression was negatively associated with ERBB2 & FGFR3 mRNA (r=-0,3021 and r=-0,3326, p<0,0001). Inverse relation of FAP expression with ERBB2 & FGFR3 was even more pronounced (r=-0,4883 and r=-0,5177, p<0,0001). Clustering validated that CXCR4 and FAP are elevated in non-luminal tumors not responding to NACT. Exemplarily one stromal rich pT2 G3 MIBC patient with elevated FAP expression, who was predicted to be unresponsive to NACT, was selected for FDG and FAP PET/CT imaging after two cycles of NACT. Indeed metastatic lesion were detected in the liver and pancreatic tissue. FAP imaging revealed to be more sensitive than conventional FDG imaging. In a next step ^{68}Ga-CXCR4 was instilled into the bladder of a patient with NACT-resistant MIBC rejecting cystectomy to establish a non-systemic approach for radioligand therapy. Theranostic instillation imaging revealed strong uptake into the invading MIBC and subsequent instillation therapy with ^{177}Lu-FAP led to partial remission and increased immune cell infiltration indicating initial effectivity. **Conclusions:** Expression of the radioligand targets CXCR4 and FAP are associated with aggressive stromal and basal like tumors being resistant to NACT. This could be validated by selecting patients for FAP & CXCR4 PET/CT imaging. Instillation of radioligands into the bladder revealed to be safe with first signs of effectivity justifying clinical approaches as part of phase 1 / 2 clinical trials. Research Sponsor: None.

Real-world treatment (tx) patterns and clinical outcomes in patients (pts) with locally advanced or metastatic urothelial carcinoma (la/mUC) in Germany: Results of a retrospective observational study (CONVINCE).

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Background: Platinum-based chemotherapy (PBC) is the standard-of-care first-line (1L) tx for pts with la/mUC (followed by avelumab 1L maintenance in pts without progressive disease since its approval in Germany in Jan 2021). This study describes demographics, tx patterns, and clinical outcomes for pts with la/mUC treated in routine clinical practice in Germany between 2019 and 2021. **Methods:** CONVINCE, a retrospective, multicenter medical chart review study, was initiated in Dec 2021 and included adult pts who received 1L tx for la/mUC between 2019 and 2021. All pts were required to have ≥6 months of follow-up data available after end/start of 1L, depending on the type of tx received. Fully anonymized data were obtained from 27 oncology or urology institutions (8 hospitals and 19 office-based practices) across Germany. Descriptive statistics were used to analyze the results, and Kaplan-Meier methods were used to compute time-to-event outcomes. Pts were classified into 3 groups: (A) PBC with end of tx between Jan 2019 and Sep 2021 and (B) immuno-oncology (IO) therapy and (C) other non-PBC tx, both with start of tx between Jan 2019 and Sep 2021. **Results:** Of 188 pts included, median age at start of 1L was 70 years, 72.3% were male, most had ECOG PS 0/1 (92.5%), and the majority (60.1%) were treated by medical oncologists. A total of 143 pts (group A) received PBC (PBC + gemcitabine, 88.1%; PBC + non-gemcitabine agents, 8.4%; and cisplatin monotherapy, 3.5%). Cisplatin + gemcitabine (82.5%) was used more often than carboplatin + gemcitabine (17.5%). Six pts were treated with avelumab 1L maintenance following PBC. In group B, 36 pts (19.1%) received IO monotherapy (atezolizumab, 44.4%; pembrolizumab, 41.7%). In group C, 9 pts (4.8%) received non-PBC tx. Clinical outcomes in groups A and B are shown in the Table. Results for group C are not shown due to small sample size. **Conclusions:** CONVINCE describes characteristics, tx patterns, and outcomes in pts with la/mUC in routine clinical practice in Germany. In adherence with tx guidelines, most pts received PBC in 1L. New IO approvals, including avelumab 1L maintenance and other novel agents, could improve outcomes in pts with la/mUC. Further real-world studies should be performed to evaluate the uptake of these options within routine care. Research Sponsor: The study was sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945) and was previously conducted under an alliance between the healthcare business of Merck KGaA, Darmstadt, Germany and Pfizer.

		Group A, PBC n=143 (76.1%)	Group B, IO n=36 (19.1%)
	Male, %	72.7	66.7
	Age at start of 1L tx, median (range), years	69 (48-84)	77 (41-87)
Outcomes	rwPFS, median, months	10.5	12.6
	rwOS, median, months	18.1	15.9
Best response	Evaluable pts, n (%)	136 (95.1)	30 (83.3)
(physician assessment)	Complete response, n (%)	19 (14.0)	6 (20.0)
	Partial response, n (%)	58 (42.6)	12 (40.0)
	Stable disease, n (%)	41 (30.1)	5 (16.7)
	Objective response rate, n (%)	77 (56.6)	18 (60.0)

rwPFS, real-world progression-free survival, rwOS, real-world overall survival.

Characteristics, treatment patterns, and clinical outcomes of patients undergoing neoadjuvant chemotherapy and radical cystectomy for muscle-invasive bladder cancer in the real world.

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Background: Muscle-invasive bladder cancer (MIBC) is characterized by an overall poor prognosis with a 5-year overall survival (OS) of ~50%. Radical cystectomy (RC) with cisplatin-based neoadjuvant chemotherapy (NAC) has demonstrated improved survival in eligible patients and is the current guideline-recommended treatment; however, NAC is underutilized in the real world. The characterization of NAC-treated patients as well as their clinical outcomes in routine practice warrants continued investigation. The objective of this study is to describe the demographic and clinical characteristics, neoadjuvant treatment patterns, and clinical outcomes of patients with MIBC undergoing RC with NAC. **Methods:** A retrospective cohort study was conducted among adult patients (≥18 years) with MIBC (T2–T4aN0M0, T1–T4aN1M0) diagnosed between 1/1/2016 and 12/31/2021, who received NAC followed by RC, selected from the Syapse Learning Health Network. Patients with another primary tumor ≤3 years prior to MIBC diagnosis, prior partial cystectomy, or prior neoadjuvant radiation were excluded. Patients were followed from NAC initiation (index date) until end of the study period (12/31/2022) or death, whichever occurred first. The analyses included descriptive statistics of demographic and clinical characteristics, NAC treatment pattern, and pathologic complete response (pCR), defined as pT0N0 per pathology reports. Kaplan–Meier analysis was used to describe OS. **Results:** A total of 140 patients with MIBC met the eligibility criteria of this study (median age 67; 73% male; 90% white; 82% current or former smokers), with a median follow-up of 34 months. Almost all (98%) patients had *de novo* MIBC and 99% had urothelial histology. At diagnosis, most patients (83%) were staged with T2N0M0 disease; the remaining patients had T1–T4aN1M0 (9.3%) or T3/4N0M0 (7.9%) disease. Median time from MIBC diagnosis to RC was 5 months and median (IQR) NAC treatment duration was 68 days (44-74). The most commonly used NAC regimen was cisplatin + gemcitabine (62.9%), followed by cisplatin + doxorubicin + methotrexate + vinblastine (30.0%). Among patients with pCR data (n=136), 29% achieved pCR. During follow-up, 21% of patients died, and median OS was not reached. Survival rates (95% CI) at 2 and 3 years were 83.8% (77.8–90.2%) and 79.7% (73–87.1%), respectively. **Conclusions:** Cisplatin-based NAC was widely utilized, with cisplatin + gemcitabine being the most commonly administered regimen. Approximately a third of patients in this neoadjuvant treated RC cohort achieved pCR. Future studies should investigate intermediate or surrogate outcomes in MIBC such as disease-free, event-free, or metastatic-free survival when mature follow-up data is unavailable. Longer follow-up is required to monitor long-term outcomes such as median overall survival. Research Sponsor: This work was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Safety and efficacy of enfortumab vedotin in patients with metastatic/locally advanced urothelial cancer: Real-world evidence from a European database.

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Background: Enfortumab vedotin (EV) is an antibody drug conjugate targeting Nectin-4. It was approved by EMA/FDA in patients (pts) with metastatic/ locally advanced urothelial cancer post platinum and immune check point inhibitors following the results of the EV-301 trial. We report updated efficacy and safety data of EV in a large European cohort of real-world pts (GUARDIANS consortium) treated in hospitals and private practices. **Methods:** Retrospective data were collected from 25 German and Swiss hospitals and private practices for pts who received EV. Adverse events (AEs) were reported according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 criteria. Objective responses were evaluated by local investigators according to Response Evaluation Criteria in Solid Tumors version 1.1. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method. **Results:** Weidentified 188 pts (32.4% female) with a median age of 66 yrs (range 31-89; 22.3% >/= 75 yrs). Eastern Cooperative Oncology Group performance status (ECOG PS) was 0/1/2/3-4/ unknown in 36/39/11/3/11%. EV was administered in the fourth or later line in 43% of pts. Overall response rate (ORR) was 46.3% (partial remission: 42.0%, complete response 4.3%), disease control rate was 58.0%. Median OS (mOS) was 12.0 months (mo) (95% confidence interval 9.65-14.35) and median PFS (mPFS) was 7.0 mo (95% confidence interval 5.43-8.57). Any-grade AEs were observed in 71% and CTCAE grade ≥3 AEs in 32% of pts. Most common AEs were peripheral sensory neuropathy (33.5% any grade), skin toxicity (24.5%) and fatigue (22.9%). In pts >/= 75 yrs, females, and pts treated in >/=4th line mOS, mPFS, ORR, and toxicities were comparable to younger and male counterparts and pts treated in <4th line, respectively. Limitations are retrospective design and short follow-up. **Conclusions:** Anti-tumor activity of EV in real-world pts including difficult-to-treat subgroups is comparable to the results of the pivotal EV-301 trial. No new safety signals were observed. Research Sponsor: None.

Patterns of concurrent chemotherapy selection in US patients undergoing trimodality therapy for muscle-invasive bladder cancer.

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Background: Trimodality therapy (TMT) consists of concurrent chemoradiation following maximal transurethral resection of the bladder tumor for muscle-invasive bladder cancer (MIBC). Current TMT treatment guidelines allow for several different radiosensitizing chemotherapy regimens, however there is limited data on existing use patterns. **Methods:** Using data from CancerLinQ Discovery, 71,499 patients with a bladder tumor diagnosed between 2000-2022 were included. Patients with documented radiation to "bladder" or "pelvis" with no known metastatic disease and a documented chemotherapy regimen started within a 30-day window of radiation, were included in the final analyses (n=233). Chemotherapy regimens included cisplatin, gemcitabine, 5FU+ mitomycin, taxanes, and other. Through bivariate analyses, patient characteristics and TMT treatment patterns were characterized. **Results:** The most commonly utilized TMT chemotherapy regimen was cisplatin alone (42.5%) followed by gemcitabine (19.3%), 5FU+ mitomycin (15.8%), taxanes (12.5%) and other (9.9%). These data demonstrated a significant relationship between age at diagnosis and chosen TMT regimen (p=0.017). Patients <65 were more likely to receive cisplatin (27.3%), 5FU mitomycin (29.7%) or other (30.4%) while patients 85+ were more likely to receive gemcitabine (28.9%). Patients more frequently received cisplatin alone prior to 2017 (before 2011: 28.3% vs. 2011-2016: 53.5% vs. 2017-2022:18.2%, p-value <.001), with a trend towards more gemcitabine use in the most recent period between 2017-2022 (51.1% vs. before 2011: 20.0% vs 2011-2016: 28.9%, p-value <.001). Additionally, there was less taxane use over time (before 2011: 37.9% vs. 2011-2016: 55.2% vs 2017-2022: 6.9%, p-value <.001). Finally, the association between TMT regimen and Charlson Comorbidity Index (CCI) trended toward significance—those treated with cisplatin alone were most likely to have a CCI of 0 (62.6%, p-value = 0.081) while patients receiving gemcitabine alone or 5FU + mitomycin were more likely to have a CCI of 1+ (gemcitabine alone: 51.1%, 5FU + mitomycin 51.4%, p-value = 0.081). **Conclusions:** There remains wide variation in the use of chemotherapy regimens in TMT with cisplatin monotherapy as the most utilized radiosensitizing agent overall. Since 2000, there has been a shift away from taxane therapy and increased gemcitabine use. Patients with lower CCI had a trend to more frequently receive cisplatin and older patients more frequently received gemcitabine. Further investigations are needed to better characterize patient characteristics as well as toxicity and survival by drug regimen to better help inform treatment guidelines. Research Sponsor: Kathleen Allison in memory of Tom Allison.

Economic burden of radical cystectomy and trimodal therapy for bladder cancer in the United States: Real-world study.

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Background: Bladder cancer (BC) is exponentially deadly once it invades muscle, with the highest per patient treatment costs among cancers. Radical cystectomy (RC) and trimodal therapy (TMT) are recommended treatment options for muscle-invasive BC. This study describes patient/treatment characteristics and short- and long-term costs/healthcare utilization (HCU) associated with RC and TMT. **Methods:** Patients with BC undergoing RC or TMT were identified using Optum claims data (October 2015-April 2023). Incident cases were captured, and individuals diagnosed with a prior BC, secondary bladder neoplasm, and non-bladder malignancies were excluded. Costs and HCU (e.g., inpatient, outpatient, emergency, pharmacy) were evaluated up to 5 years of follow-up. **Results:** Median [IQR] ages of the RC (N=839) and TMT (N=484) cohorts were 71 [66-76] and 75 [69-81] years, and NCI comorbidity index was 0.50±0.43 and 0.52±0.45, respectively. Median follow-up durations were 30 [19,47] and 32 [20,48] months for RC and TMT patients, respectively. Median cost and HCU per patient in the RC cohort were $70,671 [$55,878-$106,812] with 26 [16-39] visits in 3 months, $103,579 [$71,12-$158,489] with 56 [39-86] visits in 12 months and increased to $211,671 [$138,597-$346,389] with 163 [119-218] visits in 60 months. For TMT, median cost and HCU per patient were $34,612 [$16,705-$64,263] with 19 [12-33] visits in 3 months, $116,259 [$65,300-$188,622] with 72 [46-94] visits in 12 months, and increased to $274,462 [$186,337-$421,534] with 186 [144-238] visits in 60 months (N=72). Outpatient care was the highest cost contributor for both cohorts across all time periods, except the first 3 months for RC, where inpatient care was predominant. Approximately 25% (N= 211) of patients received neoadjuvant chemotherapy before RC. For patients receiving TMT, median radiotherapy fractions delivered was 36 [18-43], and 8.1% underwent salvage RC. **Conclusions:** The burden of RC or TMT-treated BC patients remains high, suggesting key targets for cost containment to optimize value-based care. However, our costs are lower compared to previous literature, possibly due to 3rd party payer (i.e., closed networks), treatment advancements, and patient selection. Future research should evaluate the cost and HCU implications of guideline-recommended treatments i.e., neoadjuvant chemotherapy followed by RC vs. TMT with advised chemotherapy type/duration for both. Research Sponsor: None.

Median cost per patient (2022 USD).

Follow-up (months)	RC	TMT
3		
N	839	484
Median [IQR] ($)	70,671 [55,878-106,812]	34,612 [16,705-64,263]
12		
N	839	484
Median [IQR] ($)	103,579 [71,121-158,489]	116,259 [65,300-188,622]
24		
N	532	321
Median [IQR] ($)	123,773 [82,681-189,878]	169,219 [93,230-287,991]
48		
N	202	124
Median [IQR] ($)	180,826 [125,064-307,115]	259,740 [144,293-395,779]
60		
N	103	72
Median [IQR] ($)	211,671 [138,597-346,389]	274,462 [186,337-421,534]

Cost-effectiveness-analysis of different treatment modalities in bacillus Calmette-Guérin (BCG) unresponsive non-muscle invasive bladder cancer (NIMBC).

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Background: Elaborate treatment and repetitive surveillance makes bladder cancer to the most expensive cancer type over the lifetime of a patient with a peak in non-muscle invasive bladder cancer. Radical cystectomy (RC) as the Standard of Care in BCG unresponsive NMIBC is associated with a significant health-related quality-of-life burden (QALY). Gemcitabine/Docetaxel, Pembrolizumab or Hyperthermic Intravesical Chemotherapy (HIVEC) have recently been published as salvage treatment options trying to increase the rate of bladder preservation. **Methods:** We developed a Markov model from a payer´s perspective with the clinical data of single-arm studies for BCG unresponsive NMIBC (Gemcitabine/Docetaxel and Pembrolizumab) and our clinical data for patients receiving HIVEC (n=29) as intravesical salvage-chemotherapy. Costs were simulated with a non-commercial DRG-grouper, utilities were derived from comparable cost-effectiveness studies. We used a Monte-Carlo Simulation to identify the optimal treatment, comparing the incremental cost effectiveness ratios (ICER) in consideration of a willingness-to pay of 50.000 Euro/QALY. **Results:** Over a horizon of 10 years, Gemcitabine/Docetaxel, HIVEC and Pembrolizumab were associated with costs of 48.353 64.438 and 204.580 Euro, and QALY´s of 6.16, 6.48 and 6.00, resulting in an ICER of 26.482, 42.567 and 184.533 Euro in comparison to RC (costs: 21.871 Euro; QALY: 5.01). Monte-Carlo Simulation has identified HIVEC as the treatment of choice in the assumption of a WTP of <50.000 Euro. QALY gains in Gemcitabine/Docetaxel and especially HIVEC were mainly driven by bladder preservation and the low rate of progression. **Conclusions:** Considering a WTP of <50.000 Euro / QALY, Gemcitabine/Docetaxel and HIVEC are highly cost-effective therapy options in BCG unresponsive bladder cancer, while RC remains the cheapest option. At its current price, Pembrolizumab is only cost-effective with a price reduction of 70%. Research Sponsor: None.

Avelumab first-line maintenance (1LM) in patients (pts) with locally advanced or metastatic urothelial carcinoma (la/mUC) in the Czech Republic: Interim real-world results from a national reimbursement registry.

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Background: Avelumab 1LM treatment is recommended by international guidelines as the standard of care for pts with la/mUC that has not progressed with 1L platinum-based chemotherapy (PBC) and has been approved in the EU since Jan 2021. In the Czech Republic, following EU approval, there is a requirement to provide real-world data for "highly innovative medicinal products" such as avelumab 1LM when reimbursement decisions are temporary. Obtaining reimbursement therefore requires the creation of a registry to collect real-world data. We report interim results from a retrospective analysis of a national reimbursement registry for avelumab 1LM in the Czech Republic. **Methods:** Registry data were collected by the Office of Health Insurance (KZP) for pts with la/mUC receiving avelumab 1LM in the Czech Republic between Oct 2021 and Jan 2023. The primary endpoint was overall survival (OS) from the start of avelumab 1LM (index date); secondary endpoints included progression-free survival (PFS) from the start of avelumab 1LM and safety. Descriptive statistics were used to analyze the data. OS and PFS were estimated using the Kaplan-Meier method. **Results:** 59 eligible pts with la/mUC were treated and documented. At data cutoff (Jan 3, 2023), median follow-up was 6.1 mo (range, 0-16.5). All pts were White; 43 were male and 16 were female. At the start of avelumab 1LM, median age was 71 y (range, 49-84) and 22 pts (37.3%) had visceral metastases. 1L PBC was cisplatin-based in 30 pts (50.8%), carboplatin-based in 24 (40.7%), and both (switched from cisplatin to carboplatin) in 5 (8.5%). Best response to 1L PBC was complete response in 5 pts (8.5%), partial response in 30 (50.8%), and stable disease in 24 (40.7%). Median time from the end of PBC to the start of avelumab was 4.1 wk (range, 1.0-44.0). Effectiveness data for avelumab 1LM are shown in the Table. OS and PFS data are immature, with only 14 pts (23.7%) having died or had disease progression at the time of analysis. 10 adverse events were reported in 9 pts (15.3%), including grade 3 infusion-related reaction (1 pt), grade 2 diarrhea (2 pts), and grade 2 nephritis, pneumonitis, and Addison disease (1 pt each). At last evaluation, 53 pts were alive, of whom 5 pts had started subsequent treatment. **Conclusions:** This is the first study of pts with la/mUC treated with avelumab 1LM in a real-world setting in the Czech Republic. These preliminary data agree with the results of the phase 3 JAVELIN Bladder 100 trial and other real-world studies, confirming the effectiveness and manageable safety profile of avelumab 1LM in la/mUC. Follow-up for OS is ongoing. Research Sponsor: Merck spol. s r.o., Prague, Czech Republic, an affiliate of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

Effectiveness data for avelumab 1LM	N=59
Median OS, mo	NR
OS rate (95% CI), %	
6 mo	93.1 (85.8-100)
12 mo	78.6 (63.4-97.5)
Median PFS, mo	NR
PFS rate (95% CI), %	
6 mo	75.9 (63.7-90.4)
12 mo	55.0 (37.5-80.6)

NR, not reached.

Subgroup analyses from READY: Real-world data from an Italian compassionate use program (CUP) of avelumab first-line maintenance (1LM) treatment for locally advanced or metastatic urothelial carcinoma (la/mUC).

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Background: A multicenter CUP provided early access to avelumab 1LM in Italian patients (pts) with Ia/mUC before reimbursement. Real-world pt characteristics and outcomes with avelumab 1LM from READY were reported previously. Here, we report updated data and subgroup analyses of effectiveness with avelumab 1LM. **Methods:** This prospective, noninterventional CUP included pts with la/mUC who were progression free after 1L platinum-based chemotherapy (PBC; 4-6 cycles, starting avelumab 1LM 4-10 wk after last PBC dose). Pts were enrolled from Jan 18, 2021 to Mar 7, 2022. Avelumab was provided per physician request and after approval by local ethics committees, per Italian compassionate-use regulations. Pts who had a relapse within 12 mo of prior adjuvant or neoadjuvant systemic therapy, including immune checkpoint inhibitors, were excluded. **Results:** 464 pts were included (78.45/21.55% male/female; median age, 70.0 y [interquartile range, 63.0-76.0]). At data cutoff (July 30, 2023), median follow-up from start of avelumab 1LM in 411 evaluable pts was 20.24 mo (95% CI, 19.78-20.93); median overall survival (OS) and progression-free survival (PFS) from start of avelumab were 26.22 mo (95% CI, 19.97-not estimable [NE]) and 7.63 mo (95% CI, 5.79-9.24), respectively. In pts aged <60 y (n=53), 60-70 y (n=150), and >70 y (n=208), median OS (95% CI) was not reached (NR; 12.86 mo-NE), NR (24.21 mo-NE), and 24.01 mo (16.94-NE), and median PFS was 5.20 mo (2.83-6.71), 7.70 mo (5.26-10.07), and 8.82 mo (6.05-12.93), respectively. In pts who received 1L cisplatin + gemcitabine (n=183) and 1L carboplatin + gemcitabine (n=219), median OS (95% CI) was NR (16.05 mo-NE) and 25.10 mo (19.97-NE), and median PFS was 6.61 mo (5.30-9.18) and 8.42 mo (6.05-12.73), respectively. The table shows OS and PFS in other subgroups defined by best response to 1L PBC and number of 1L PBC cycles received. **Conclusions:** Real-world outcomes with avelumab 1LM in this CUP in Italy show clinical benefit across various subgroups. These data are clinically relevant and are consistent with other real-world country-based studies and the phase 3 JAVELIN Bladder 100 trial. Findings further support the use of avelumab 1LM as standard of care in pts with la/mUC who are progression free after PBC. Research Sponsor: The study was sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945) and was previously conducted under an alliance between the healthcare business of Merck KGaA, Darmstadt, Germany and Pfizer.

		OS		PFS	
	n	Median (95% CI), mo	12-mo rate (95% CI), %	Median (95% CI), mo	12-mo rate (95% CI), %
Best response to 1L PBC					
Complete response	41	NR (24.21-NE)	87.4 (77.19-97.53)	22.24 (8.13-NE)	56.1 (40.91-71.29)
Partial response	233	26.22 (21.22-NE)	69.1 (63.16-75.03)	8.42 (5.39-11.71)	42.4 (36.07-48.76)
Stable disease	137	13.65 (10.56-NE)	53.1 (44.71-61.42)	5.90 (4.87-6.74)	35.2 (27.24-43.24)
No. of 1L PBC cycles					
4	203	19.97 (13.65-NE)	61.8 (55.15-68.52)	6.61 (5.49-9.31)	39.5 (32.77-46.22)
6	157	NR (24.01-NE)	71.1 (63.99-78.17)	8.29 (5.13-15.63)	44.5 (36.75-52.29)

Evolving treatment landscape in metastatic urothelial carcinoma (mUC) post-avelumab maintenance approval: Real-world insights from The US Oncology Network.

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Background: Locally advanced/metastatic urothelial carcinoma (mUC) has poor prognosis and disproportionately affects the elderly, who often have coexisting illness and limited treatment options. According to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Bladder Cancer (v3.2023), platinum-based chemotherapy (PBC) followed by avelumab maintenance therapy (maintA, only if there is no progression on first-line [1L] PBC), pembrolizumab (P, for platinum-ineligible), and P in combination with enfortumab vedotin (P+EV, for cisplatin-ineligible) are the preferred regimens. We evaluated real-world treatment patterns and overall survival (OS) among mUC patients during the period between maintA and P-EV approvals in the US. **Methods:** This retrospective cohort study was conducted using structured and chart review data from iKnowMed (iKM), The US Oncology Network electronic health record database. The cohort included adult mUC patients diagnosed between 30 April 2020 and 30 June 2021. Patients were followed from index date (date of 1L anticancer treatment) through 31 March 2023, last patient record or death, whichever occurred first. MaintA was defined as receiving avelumab after 1L PBC, with no documented progressive disease prior to avelumab start or as maintenance therapy indicated by physician notes. Descriptive statistics were used to report patient characteristics and treatment patterns. Kaplan-Meier analysis was implemented to assess OS. **Results:** A total of 207 patients initiated 1L treatments. The median age was 74 (range: 46 - 90+) years and 166 (80.2%) were male. Of 207 1L-treated patients, 107 (51.7%) received immune checkpoint inhibitor (ICI) monotherapy, 80 (38.6%) received PBC, and 20 (9.7%) received other treatments. The use of 1L ICI monotherapy increased with age, ranging from 15 (14.0%) among those younger than 65 to 57 (53.3%) among those aged 75 or older. Of patients who received 1L PBC, 28 (35.0%) received ICI maintenance therapy; majority of these (n = 26, 92.9%) received maintA (32.5% of patients received 1L PBC). During the follow-up, 71 (34.3%) patients received 2L treatment and 25 (12.1%) patients received 3L treatment. Majority of patients in 2L settings received antibody drug conjugates (n = 30, 42.2%) or ICI monotherapy (n = 27, 38.0%). Median (95% confidence interval) OS was 12.6 (8.5, 15.1) months for 1L-treated patients overall. **Conclusions:** Despite many recent advances in the therapy for mUC, these patients had poor prognosis. Notably, many 1L patients did not have the opportunities to receive 2L+ treatment, which demonstrated continuing unmet need for mUC patients. ICI monotherapy continues to be a prevalent option, especially for older patients. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Updated results from AVENANCE: Real-world effectiveness of avelumab first-line maintenance (1LM) in patients (pts) with advanced urothelial carcinoma (aUC) and analysis of subsequent treatment.

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Background: Avelumab 1LM is the standard of care for aUC that has not progressed with 1L platinum-based chemotherapy based on level 1 evidence from the JAVELIN Bladder 100 phase 3 trial. Previous results from AVENANCE showed the effectiveness and safety of avelumab 1LM in a real-world population with aUC in France. We report updated data and analyses by subsequent (next-line) treatment. **Methods:** AVENANCE (NCT04822350) is a noninterventional, ambispective study. Eligible pts had aUC that had not progressed with 1L platinum-based chemotherapy and previous, ongoing, or planned avelumab 1LM treatment. The primary endpoint is overall survival (OS). Data reported are preliminary, and analysis is ongoing. **Results:** 594 pts were analyzed. At data cutoff (May 31, 2023), median follow-up was 24.2 mo (range, 0.6-43.7); 142 pts (23.9%) remained on avelumab. Median duration of avelumab treatment was 5.6 mo (95% CI, 4.9-6.9). Reasons for discontinuation were disease progression in 330 (73.2%), adverse event in 50 (11.1%), death in 42 (9.3%), and other reasons in 29 (6.4%) pts. 314 pts (52.9%) received subsequent treatment after avelumab: chemotherapy in 238 (75.8%), antibody-drug conjugate (ADC) in 52 (16.6%; enfortumab vedotin, 46 [14.6%]; other, 6 [1.9%]), immunotherapy in 12 (3.8%), and other in 12 (3.8%). Characteristics of pts who received ADC or chemotherapy are shown (Table). In the overall population, median OS from start of avelumab 1LM was 21.1 mo (95% CI, 17.3-23.8), and 1- and 2-y OS rates (95% CI) were 66.58% (62.57%-70.26%) and 45.41% (40.89%-49.82%), respectively. In pts who received subsequent ADC or chemotherapy, median OS (95% CI) from start of avelumab 1LM was 31.3 mo (22.2-not estimable) and 14.0 mo (13.2-15.6), 1-y OS rates (95% CI) were 85.93% (72.72%-93.04%) and 61.68% (55.13%-67.56%), and 2-y OS rates were 66.90% (49.85%-79.29%) and 25.43% (19.17%-32.14%), respectively. **Conclusions:** Updated results from the AVENANCE study confirm the effectiveness of avelumab 1LM in a real-world population. In pts with subsequent treatment (≈70% of pts who discontinued), a contemporary sequence of ADC after 1L platinum-based chemotherapy and avelumab 1LM treatment showed encouraging OS. Clinical trial information: NCT04822350. Research Sponsor: None.

	Subsequent Treatment	
	ADC (n=52)	Chemotherapy (n=238)
Age, median, y	72.6	72.9
ECOG performance status, %		
0	23.8	28.9
1	61.9	52.2
≥2	14.3	18.9
Primary tumor site, %		
Lower tract	78.8	79.3
Upper tract	21.2	20.7
Prior treatment for localized UC, %		
28.8	34.6	
Disease stage, %		
Metastatic	96.2	94.9
Locally advanced	3.8	5.1
1L chemotherapy, %		
Carboplatin + gemcitabine	61.5	63.8
Cisplatin + gemcitabine	28.8	23.4
ddMVAC	3.8	5.1
Other or switched	5.8	7.7
Response to 1L chemotherapy, %		
Complete response	21.2	17.5
Partial response	53.8	57.3
Stable disease	19.2	23.5
Other	5.8	1.7

ddMVAC, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin.

Treatment (Rx) trends and attrition with lines of therapy in patients (pts) with advanced urothelial carcinoma (aUC).

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Background: The Rx landscape of aUC has evolved significantly with the approval of novel therapeutic agents. However, even with the advent of new therapeutic options, aUC remains a lethal malignancy with poor outcomes. Here, we use a large real-world database to describe Rx trends and attrition in pts with aUC. **Methods:** Patient data was extracted from the Flatiron Health EHR-derived deidentified database. Inclusion criteria: pts with histological diagnosis of metastatic or aUC between 1/1/11-1/10/2023 and Rx receipt at participating site. Pts receiving Rx for two or more cancers were excluded. Rx were grouped into categories based on NCCN approved regimens. Rx in each line (L) of therapy were summarized using frequency and percentages. All the analysis was done using R version 4.2.3. **Results:** Of the identified 12,157 pts in the dataset, 8,660 had Rx information and 7,260 were included in the analysis based on eligibility criteria. Details of each line of therapy are presented in the table. Of all pts receiving 1L, only 37% receive 2L and only 12% receive 3L of therapies. Carboplatin containing regimen were most commonly used in 1L followed by PD-1/L1 therapies. PD-1/L1 therapies were most commonly used regimens in 2L and 3L. Over time, there has been a steady decline in the overall use of platinum-based regimens, and since 2015 an increase in uptake of PD-1/L1 agents has been observed. The use of novel therapeutic agents, such as enfortumab vedotin (EV), erdafitinib, and sacituzumab govitecan (SG), has increased since 2019, especially in the 2L and 3L of therapy. **Conclusions:** Approximately two-thirds of aUC patients don't receive 2L or beyond systemic therapy. Majority of real-world patients (61%) did not receive cisplatin-based regimens and instead received carboplatin or PD- 1/L1i based therapies. These data warrant the need for more effective and tolerable Rx in front-line setting. Research Sponsor: None.

Rx	1L n (%)	2L n (%)	3L n (%)	4L n (%)	5L n (%)	6L n (%)
	7260 (100)	2714 (37.4)	857 (11.8)	282 (3.9)	81 (1.1)	27 (0.4)
Carboplatin based regimen	2241 (30.9)	403 (14.8)	106 (12.4)	28 (9.9)	7 (8.6)	2 (7.4)
Cisplatin based regimen	2008 (27.7)	157 (5.8)	48 (5.6)	10 (3.5)	0 (0.0)	2 (7.4)
PD-1/L1	2174 (29.9)	1412 (52.0)	258 (30.1)	75 (26.6)	13 (16)	5 (18.5)
Single agent non-platin chemotherapy	565 (7.8)	342 (12.6)	169 (19.7)	47 (16.7)	23 (28.4)	7 (25.9)
Enfortumab vedotin	57 (0.8)	219 (8.1)	159 (18.5)	62 (22)	13 (16)	2 (7.4)
Erdafitinib	14 (0.2)	39 (1.4)	28 (3.3)	8 (2.8)	4 (4.9)	3 (11.1)
Sacituzumab govitecan	6 (0.1)	14 (0.5)	34 (4.0)	27 (9.6)	15 (18.5)	1 (3.7)
Other	195 (2.7)	128 (4.7)	55 (6.4)	25 (8.9)	6 (7.4)	5 (18.5)

Role of geriatric assessment and oncological multidimensional prognostic index (Onco-MPI) in a real-world cohort of elderly patients with advanced urothelial carcinoma.

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Background: At least 75% of bladder cancer (BC) are diagnosed in adults aged ≥65 years, with a median of 72 years. Older adults have poor outcomes but are also an heterogeneous population in which the functional status often does not reflect the chronological age. ASCO and SIOG recommend the use of geriatric assessment (GA) to guide management of these patients (pts) but very few data are present to date. **Methods:** We investigated the role of GA and an oncological version of MPI in pts ≥70 years old affected by advanced/metastatic urothelial carcinoma. Data were retrieved from a prospectively maintained database from 2010 to 2022. Comprehensive GA (CGA) is a multidimensional tool used to classify pts as fit, vulnerable and frail according to Balducci's criteria. Onco-MPI was calculated by a validated algorithm derived from different GA domains and tumour characteristics. We also collected characteristics of pts, tumors and treatment regimens. Correlation between GA and treatments used and oncological outcomes were analysed. **Results:** Complete data and follow up were available for 181 patients. Pts characteristics are reported in Table 1. According to Onco-MPI all the pts but 7 were at high risk. The mFU was 46.2 months, while mOS was 8.2 months. Balducci's CGA and Bellmunt groups had a concordance of 58%, $p<0.01$. Strong correlations between these scores and type of treatment received were found (pts fit or 0 score received more often a platinum-based treatment without reduction dose while frail or 2-3 score received more often treatment with a reduced dose or no treatment at all, $p<0.01$). The two scores have a strong prognostic value (18.5 vs 10.8 vs 3.8 months, $p<0.01$; 21.9 vs 8.5 vs 4.1 months, $p<0.01$, respectively for CGA and Bellmunt subgroups). At univariate analysis also timing of mets, number of sites, type of treatment and dose were good prognostic variables. All these variables retained their prognostic value at a multivariate analysis incorporating each of the two scores separately. **Conclusions:** CGA has a great prognostic value in older adults with metastatic urothelial cancer. This tool could help in decision making and patients stratification but validation in prospective cohort is needed. Onco-MPI could also be useful but new cut offs must be set in this specific population.
Research Sponsor: None.

Pts characteristics.

Characteristics		Number (%)
Age	70-75 / 76-79 / ≥80 year old	60 (33.2) / 58 (32.0) / 63 (34.8)
CGA class	fit / vulnerable / frail	59 (32.6) / 49 (27.1) / 73 (40.3)
Bellmunt score	0 / 1 / 2-3	49 (27.1) / 65 (35.9) / 67 (37.0)
Timing of metastasis	synchronous / metachronous	80 (44.2) / 101 (55.8)
Site of the primitive	bladder / upper tract	134 (74.0) / 47 (26.0)
Number of metastatic sites	1 / 2 / ≥3	69 (38.1) / 79 (43.7) / 33 (18.2)
Treatment received	none / Platinum based / ICI / Non platinum based	64 (35.3) / 99 (54.7) / 13 (7.2) / 5 (2.8)

Geriatric assessment (GA) in elderly patients with urothelial cancer (UC): Can GA select frail patients and avoid toxic treatment? Multidisciplinary single center experience.

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Background: UC is a disease of the elderly. Median age at UC diagnosis is olderthan for other major tumours (73 years old). The correct management of UC in the elderly remains controversial. Treatment-decisions should be based on biological age, not in chronological one. The role of geriatric assessment (GA) evolution is potentially beneficial. It has been detected between 10% to 25% frailty patients aged over 65 years are characterised as frail on GA on other tumors. GA has not been studied prospectively in UC patients. Objective: to assess the paper of GA in elderly patients with UC patients attended in an outpatient medical oncology consultation. To confirm that GA can detect at least 25% of frailty patients unsuitable for active treatment. **Methods:** Prospective interventional study. GA was done by a Geriatrician at patient's home. Treatment-decisions were based on GA results, physician choice and patients/caregivers goals. Population: patients $\geq$ 70 years old sent from January 2019 to September 2023 diagnosed with UC. Patients unsuitable to be ambulatory (Performance status PS $\geq$ 3) were excluded. Ethics review board approved the analysis. All participants signed informed consent. **Results:** 82 patients were aged $\geq$ 70 years old (57% of all patients attended). Table shows patient's information. GA detected 24 (30%) of frailty patients. They were elder, former smokers, had worse PS and worse overall survival in all stages. Non frail patient received active treatment. Comorbid and polypharmacy population was found in all three GA groups. More fit and vulnerable patients were treated with cisplatin by GA assessment than if we have applied Galsky criteria. This suggests than the strict use of a CrcL $<$ 60 ml/min is still controversial. **Conclusions:** In a very selected population, GA can still find 30% of frail patients unsuitable for treatment. Frailty seems to be a predictive and prognostic factor in elderly patients with UC. Treatment selection based on GA increase the number of patients suitable for platinum treatment. Defining "platinum-ineligible" patients with metastatic urothelial cancer should be reviewed. Selection bias cannot be excluded from our analysis. Research Sponsor: None.

Characteristics of patients (pts) with muscle-invasive urothelial carcinoma (MIUC) who received adjuvant nivolumab (NIVO) or adjuvant platinum-based chemotherapy (CHEMO) in the real-world (RW) setting.

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Background: NIVO has shown promise as an adjuvant treatment for MIUC. In the CheckMate 274 trial, NIVO achieved a significant improvement in disease-free survival compared to placebo in MIUC pts at high risk of recurrence following radical surgery. However, it is unclear how treatment decisions are made in the RW setting and what factors drive providers in selecting either NIVO or CHEMO as adjuvant treatment. We compared the baseline demographic and clinical characteristics of pts with MIUC who received adjuvant NIVO to those who received adjuvant platinum-based CHEMO in the RW setting. **Methods:** This retrospective medical chart review included pts diagnosed with stage II-IIIB MIUC who initiated treatment with NIVO or CHEMO within 120 days of radical resection between 9/1/2021 and 11/25/2022. Treating oncologists from a US nationally representative network abstracted pts' data from electronic medical charts. Pts' demographic and clinical characteristics were assessed. **Results:** Age, sex, and race were similar across cohorts (Table). Pts who received adjuvant NIVO (n = 158) vs CHEMO (n = 88) were more likely to have ECOG-PS≥ 2 at treatment initiation (24.1% vs 17.1%; P = 0.02), and more likely to receive PD-L1 testing (Not tested: 36.1% vs. 47.7%; $P < 0.0001$) and have PD-L1 expression levels ≥ 50% (13.9% vs 1.1%; $P < 0.0001$). A higher proportion of pts who received NIVO vs CHEMO had diabetes with chronic complications (15.8% vs 5.7%; P = 0.02) and hypertension (20.9% vs 6.8%; P = 0.004), and were determined to be cisplatin-ineligible (41.8% vs 25%; P = 0.007), predominately based on creatinine clearance (< 60 mL/min: 48.7% vs. 34.1%; P = 0.002) and poor PS (13.9% vs. 4.6%; P = 0.07); rheumatologic disease was less common among the NIVO cohort (1.9% vs 11.4%; P = 0.002). **Conclusions:** This RW analysis demonstrated that pts with MIUC who received adjuvant NIVO had greater baseline disease severity and comorbidities than those who received adjuvant CHEMO. These findings suggest that patient characteristics influence treatment selection of adjuvant therapy in this patient population, highlighting the need to adjust for baseline characteristics in future comparative analyses. Research Sponsor: Bristol Myers Squibb.

Characteristics among pts with MIUC who received adjuvant NIVO or adjuvant platinum-based CHEMO.

Type of Treatment Received (n, %)	NIVO N = 158	CHEMO N = 88	*P*-value
NIVO	158 (100)	—	
DDMVAC	—	9 (10.2)	
Gemcitabine/cisplatin	—	53 (60.2)	
Gemcitabine/carboplatin	—	26 (29.6)	
Age at MIUC diagnosis (median, range)	67.6 (44.0-92.6)	66 (49.4-79.8)	0.23
Male (n, %)	106 (67.1)	61 (69.3)	0.720
African-American (n, %)	42 (26.6)	24 (27.3)	0.91
ECOG ≥ 2 (n, %)	38 (24.1)	15 (17.1)	0.02
Cisplatin eligible (n, %)	85 (53.8)	65 (73.9)	0.007

Pathologic and survival outcomes following radical cystectomy for “progressive” and “de novo” muscle-invasive bladder cancer: A meta-analysis stratified by neoadjuvant chemotherapy status.

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Background: Muscle-invasive bladder cancer (MIBC) can present as de novo MIBC (dnMIBC) or progressive MIBC (pgMIBC), the latter occurring in patients with a history of non-muscle-invasive bladder cancer (NMIBC). Retrospective cohort studies have reported varied survival outcomes following RC for pgMIBC versus dnMIBC.Here we aim to pool previous studies and compare survival and pathologic outcomes in patients with pgMIBC and dnMIBC following radical cystectomy (RC), with an investigation of the impact of neoadjuvant chemotherapy (NAC). **Methods:** A comprehensive literature search was conducted on PubMed and EMBASE databases to identify studies comparing pgMIBC to dnMIBC. Survival outcomes, including cancer-specific survival (CSS), overall survival (OS), and recurrence-free survival (RFS), as well as pathologic outcomes following surgery (rates of ≤pT1, pT0, pT3/T4, and pN+ disease) were compared between pgMIBC and dnMIBC. **Results:** The analysis included 19 cohorts from 16 studies, categorized into three groups based on NAC status: 1. patients who underwent RC following completion of NAC (RC + NAC only group); 2. patients who underwent RC, with or without NAC (RC +/- NAC group); 3. patients who only underwent RC without NAC (RC only group). Compared to dnMIBC, pgMIBC demonstrated worse outcomes for CSS, OS, and RFS. In the RC + NAC only group (3 cohorts), the hazard ratio (HR) for CSS was 1.52 (95% confidence interval [CI] = 1.05-2.2), the HR for OS was 1.46 (95%CI = 1.05-2.02). Similarly, in the RC +/- NAC group (6 cohorts for CSS and 3 cohorts for OS), the HR for CSS was 1.27 (95%CI = 1.05-1.55), and the HR for OS was 1.27 (95%CI = 1.08-1.51). There were no significant differences observed in pathologic outcomes, including rates of ≤pT1, pT0, and pT3/T4 disease, across all subgroups. However, pgMIBC was associated with a higher risk of nodal metastatic (pN+) disease in the RC + NAC only group (4 cohorts, relative risk [RR] = 1.43, 95%CI = 1.12-1.84). **Conclusions:** The findings highlight the potentially worse prognosis in patients with pgMIBC compared to dnMIBC, even with the modern use of NAC. The study emphasizes the importance of careful patient counseling, further classification of patients for treatment selection, and the consideration of additional or innovative systemic therapies for pgMIBC. Research Sponsor: None.

Evaluating outcomes of sacituzumab govitecan (SG) in patients with urothelial cancer (UC), previously treated with enfortumab vedotin (EV).

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Background: SG is an antibody drug conjugate (ADC) FDA approved for treatment refractory UC with Response Rate (RR) of 27%. Many patients (pts) receive SG after disease progression (PD) on EV, another ADC commonly used in earlier lines of therapy. In the TROPHY study, 10/113 pts treated with SG received prior EV and RR was similar to that of the entire cohort. We present a real-world experience in pts treated with SG after EV. **Methods:** In this retrospective analysis, pts with aUC treated with SG following EV at Johns Hopkins were identified. Demographic and treatment details were extracted by chart review. RR [Complete Response (CR) + Partial Response (PR)] with 95% Confidence Interval (95%CI) were compared between pts who did and did not have response to EV and between subgroups of interest using the χ^2 test. Response to EV was defined as physician-assessed CR or PR. Cox proportional hazard model analysis was used for comparing progression free (PFS) and overall (OS) survival for SG between groups. **Results:** 23 pts were identified, including 10 (43.5%) females and 19 (82.6%) white. Median age was 71.8 years (range: 46.3, 85.4). Primary tumor location was upper tract for 11 (47.8%) pts, lower tract for 11 (47.8%) and 1 pt had tumor in both sites. 11 (47.8%) pts had liver metastasis present at SG initiation. SG was 3rd line treatment for 5 (21.7%) pts and $\geq$ 4th line for 18 (78.3%). 4 (17.4%) pts had tumors with variant histology. RR for the entire cohort was 17.4%. Reason for discontinuation was PD in 16 (69.6%) pts and toxicity/functional decline in 7 (30.4%). The table summarizes RR in different subgroups. Median PFS for SG was 2.63 months among EV responders and 1.35 months for non-responders [Hazard Ratio (HR): 0.31, 95%CI: 0.12, 0.83, P = 0.02]. Median OS for SG was 5.36 months in EV responders and 5.78 months in non-responders (HR: 0.82, 95%CI: 0.27, 2.46, P= 0.7). No PFS or OS difference was found between subgroups: Upper vs lower tract primary tumor, liver metastasis presence vs absence, variant histology vs pure UC, estimated glomerular filtration rate (eGFR) $\geq$ 30 mL/min vs $<$ 30. The small sample precluded multivariable analysis. **Conclusions:** To our knowledge this is the largest real-world cohort of pts with UC treated with SG post EV. A trend towards improved RR and PFS for SG was noted among EV responders. In our analysis clinical outcomes remained consistently similar across all subgroups, including pts with known poor prognosis risk factors. Research Sponsor: None.

Characteristic (N)	ORR, %	95% CI	P-value
Response to EV (14)	28.6	10.0, 58.0	0.08
No Response to EV (9)	0.0	0.0, 30.0	
Lower tract only (11)	27.3	10.0, 57.0	0.27
Upper tract UC only (11)	9.1	2.0, 38.0	
Pure UC (19)	15.8	6.0, 38.0	0.66
Variant histology (4)	25.0	5.0, 70.0	
Liver metastasis at SG initiation (11)	9.0	9.0, 53.0	0.31
Liver metastasis absence at SG initiation (12)	25.0	2.0, 38.0	

Experiences of patients with bladder cancer: A comparison of urban and rural areas.

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Background: Bladder cancer patients encounter unique challenges and advantages in urban and rural environments, significantly influencing their path from diagnosis to treatment. While numerous studies explore bladder cancer from clinical and therapeutic perspectives, there is a noticeable gap in research addressing patients' experiences based on geographical locale. This study aims to bridge this gap by offering a comparative analysis of urban versus rural experiences. **Methods:** The World Bladder Cancer Patient Coalition and IQVIA formulated an online survey, designed to capture the multifaceted experiences of bladder cancer patients. Available in various languages, the survey was accessible from October 2021 to February 2022. Responses underwent systematic analysis, with parameters including gender, time since diagnosis, age, region, and disease stage, forming the sub-analytical categories. **Results:** We received a total of 1,198 responses from 45 countries. Key findings are summarized in the table, highlighting the comparative experiences of urban and rural patients. **Conclusions:** Significant disparities emerge between urban and rural bladder cancer patients. Rural patients particularly face prolonged diagnosis times, less clear communication from healthcare providers, and experience greater challenges in accessing treatment. These findings underscore the need for a re-evaluation of communication strategies and healthcare infrastructure, especially in rural areas. This research serves as a stepping stone for further investigations aimed at fostering a more patient-centric approach to bladder cancer care. Limitations to consider involve the inherent biases of online survey distribution and the possibility of certain regions being underrepresented. Research Sponsor: Astellas; AstraZeneca; Bristol Myers Squibb; Janssen; EMD Serono; Pfizer; Seagen.

Comparative experiences of urban and rural patients.

Question #	Metric	Urban (%)	Rural (%)
8	I saw a family doctor 5 or more times before diagnosis	9%	15%
10	My wait time for diagnosis was more than 3 months	23%	27%
11	"Very clear" communication from doctor about testing	56%	50%
11	"Not at all" clear communication from doctor about testing	12%	22%
30	I had had a radical cystectomy, and the doctor did not talk to me about treatments that would allow me to keep my bladder	12%	20%
25	"Very easy" for me to travel for treatment	55%	39%
25	"Quite difficult" or "very difficult" for me to travel for treatment	6%	12%

Enfortumab vedotin (EV) in cisplatin-eligible and ineligible patients with advanced urothelial cancer (aUC): A single-center experience.

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Background: Almost 50% of patients (pts) with aUC are ineligible for cisplatin-based chemotherapy, which is current first-line treatment. Cisplatin ineligibility is associated with worse outcomes, thus new promising treatment options are an unmet need. EV is an antibody drug conjugate, approved alone or in combination with Pembrolizumab for the treatment of pts with aUC. In the EV 201 study, cisplatin ineligible pts previously treated with checkpoint had a reported response rate (ORR) of 52% to EV alone. This real-world study aims to compare outcomes between cisplatin eligible and ineligible pts treated with EV monotherapy. **Methods:** This retrospective analysis of pts with aUC treated with EV monotherapy at Johns Hopkins compared investigator-assessed radiographic response to EV, progression free (PFS) and overall (OS) survival in cisplatin eligible vs ineligible pts. Cisplatin eligibility was determined by presence of ≥1 Galsky criteria: Eastern Cooperative Oncology Group Performance Status of ≥2, creatinine clearance < 60 mL/min, hearing loss ≥ Grade 2, neuropathy ≥ Grade 2 or New York Heart Association Class 3 heart failure. Patient demographics and treatment information were extracted by chart review. ORR [Complete Response (CR) + Partial Response (PR)] and Disease Control Rates (DCR) (CR + PR + Stable Disease) were compared between groups, using the χ^2 test. Multivariable Cox proportional hazard ratios adjusted for gender, race, presence of visceral metastasis and weight were used for comparing PFS and OS between groups, $p < 0.05$ was considered significant. **Results:** We identified 46 cisplatin eligible and 32 ineligible pts. The cisplatin eligible group had 36 (78.3%) white and 8 (17.4%) female pts vs 22 (68.8%) white and 12 (37.5%) females in the ineligible group. Mean age was 65.8 vs 76.3 years respectively. 16 (34.8%) cisplatin eligible pts and 12 (37.5%) cisplatin ineligible had upper tract UC. Among cisplatin eligible pts 38 (82.6%) had visceral metastasis at EV initiation vs 29 (90.6%) ineligible. Median PFS [95% Confidence Interval (95% CI)] was 5.7 months (3.8, 7.1) for cisplatin eligible pts and 3.9 (2.9, 5.5) for ineligible [Hazard Ratio (HR): 0.69, 95% CI: 0.41, 1.14, p=0.14]. Median OS (95% CI) was 9.7 (7.2, 12.0) months for cisplatin eligible pts vs 8.8 (5.8, N/A) for ineligible (HR: 0.90, 95%CI: 0.50, 1.62, p=0.7). ORR and DCR were 47.8% (34.1, 61.9) and 65.2% (50.8, 77.3) in cisplatin eligible pts vs 37.5% (22.9, 54.7) and 56.2% (39.3, 71.8) in ineligible pts (p= 0.37 and p=0.42 respectively). **Conclusions:** In this retrospective real-world study, there was no statistically significant difference in PFS, OS, ORR or DCR between cisplatin eligible and ineligible pts with aUC treated with EV. This is consistent with the excellent outcomes reported in the EV 201 study. Use of EV in aUC eliminates the artificial outcome gap defined by cisplatin eligibility. Research Sponsor: None.

Outcomes of enfortumab vedotin (EV) therapy in relation to prior immune checkpoint inhibitor (ICI) in patients (pts) with advanced urothelial cancer (aUC).

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Background: EV is FDA approved for the treatment of aUC after disease progression with chemotherapy and/or ICI, and in combination with Pembrolizumab (P) for cisplatin ineligible pts in the first line. Reported response rate (RR) for EV+P is higher than EV alone and a retrospective study showed prior ICI is associated with higher grade of EV-related skin toxicity, suggesting immunogenic interaction. Herein we evaluated whether prior ICI correlates with improved response to EV monotherapy. **Methods:** This single-center retrospective study compared outcomes between pts with aUC who were treated with ICI immediately prior to EV (iICI) vs pts who did not receive immediate prior ICI (niICI). We also evaluated outcomes in pts who received ICI at any time prior to EV, with or without intervening treatments, compared to pts who never received ICI. Demographics and treatment details were extracted through chart review. RR (Complete Response + Partial Response) were compared between groups using χ^2 test. Univariable and multivariable Cox regression models were used for comparing Progression free (PFS) and Overall (OS) survival. Multivariable models were adjusted for visceral metastasis presence and performance status (PS) at EV initiation (C1D1). **Results:** We identified 55 pts in the iICI group and 23 in the niICI. Table 1 summarizes patient characteristics. ICIs included Pembrolizumab, Atezolizumab, Nivolumab, and Avelumab. Median PFS for EV was 5.0 vs 2.0 months and OS 11.0 vs 7.1 months in iICI vs niICI group respectively. A statistically significant Hazard Ratio (HR) for PFS [HR: 1.72, 95% Confidence Interval (95CI): 1.03, 2.89, P=0.04] and OS (HR: 2.02, 95CI: 1.13, 3.60, P=0.02) was found in the univariable analysis. In the multivariable analysis HR was 1.56 (95CI: 0.91, 2.68, p= 0.11) for PFS and 1.79 (95CI: 0.97, 3.30, p=0.06) for OS. RR to EV was 43.6% (95CI: 0.33, 0.56) vs 43.5% (95CI: 0.14, 0.69), P= 0.99. In our cohort 70/78 (89.7%) pts received ICI prior to EV with or without intervening treatments. When comparing these pts to pts who never received ICI no significant difference was found in PFS, OS or RR. **Conclusions:** In our study, EV was associated with longer PFS and OS when given immediately after ICI compared to following other therapies. However, in the most parsimonious model examined, the p-value did not reach a significance threshold of $p<0.05$. Larger prospective studies are needed to better understand the mechanism behind this trend and identify the optimal sequence or combination of EV with other treatments in aUC. Research Sponsor: None.

	iICI, N=55 (%)	niICI, N=23 (%)
Age, mean (SD)	71.4 (±9.9)	67.1 (±13.1)
Female	11 (20.0)	9 (39.1)
White	43 (78.2)	15 (65.2)
Variant histology	7 (12.7)	5 (21.7)
Upper tract UC	19 (34.5)	9 (39.1)
Visceral metastasis on C1D1	44 (80.0)	23 (100.0)
Liver metastasis on C1D1	23 (41.8)	13 (56.5)
PS 0-1	45 (81.8)	20 (87.0)
PS ≥ 2	10 (18.2)	3 (13.0)

Effect of body mass index (BMI) on efficacy of immune checkpoint inhibitors (ICIs) in patients with metastatic urothelial carcinoma (mUC) in a real-world setting.

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Background: There is emerging data on the role of BMI and outcomes of ICIs in various solid tumors, with underweight pts having worse outcomes to ICIs. The effect of BMI on efficacy of ICIs in pts with mUC is not clear. **Methods:** We identified 335 adult pts with mUC at the Cleveland Clinic treated who received >/= 2 cycles of ICI with pembrolizumab (P) or atezolizumab (A) between 2015 and 2023. Patient characteristics including age, sex, race, primary site (bladder vs upper tract UC (UTUC)), tumor histology and pre-ICI treatment NLR values were collected. BMI was calculated and values were collected and compared to assess impact on overall (OS) and progression free survival (PFS) after ICI start date. BMI was broken down into four categories: underweight (BMI less than 18.5 kg/m2), normal weight (BMI between 18.5 and 24.9 kg/m2), obese (BMI 30 kg/m2 or greater) and overweight (BMI between 25 and 29.9 kg/m2). OS and PFS were estimated by Kaplan Meier method and compared using log rank test. **Results:** Median age of pts was 73 yrs (35-95) and 254 (76%) pts were males. 247 (74%) received P, 88 (26%) received A. We found that underweight pts had significantly worse OS compared to normal or higher BMI (2.32 vs 13.08 mos; p=0.001) as well a significantly worse PFS (1.61 vs 4.75 mos; p=0.02) (Table). **Conclusions:** In our large real-world cohort of pts with mUC receiving ICI, we report for the first time the effect of BMI on outcomes with ICI. Further prospective studies are warranted. Research Sponsor: None.

BMI	N	Median OS mos (95% CI)	p-value	Median PFS mos (95% CI)	p-value
Normal	116	13.08 (9.86, 15.21)	0.001	4.75 (3.42, 6.01)	0.02
Obese	86	14.46 (8.51, 23.2)		5.83 (3.42, 10.05)	
Overweight	119	16.03 (12.85, 26.02)		5.29 (4.11, 7.33)	
Underweight	12	2.32 (1.81, NA)		1.61 (1.38, NA)	

Comparative cost-effectiveness of trimodal therapy and radical cystectomy for management of muscle-invasive bladder cancer.

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Background: Bladder preservation with trimodal therapy (TMT), which consists of maximal transurethral resection of bladder tumors followed by chemoradiation, is now included in guidelines with radical cystectomy (RC) as options for definitive management of muscle-invasive bladder cancer (MIBC). Prospective randomized controlled trial data to help guide treatment selection are lacking, and prior efforts to bridge this knowledge gap have failed primarily due to poor accrual. A recent retrospective analysis comparing TMT to RC reported similar oncologic outcomes between these treatments when performed in highly selected patients. However, treatment toxicities and costs vary significantly between these management options. To investigate the impact of these outcomes on relative treatment value, we evaluated the comparative cost-effectiveness of TMT and RC for treatment of MIBC. **Methods:** Cost-effectiveness was compared between TMT and RC for patients with a solitary, muscle-invasive tumor less than 7cm, no or unilateral hydronephrosis, limited carcinoma in situ, and adequate bladder function (criteria utilized in a recent retrospective comparative series) using a microsimulation model with a 5-year horizon from a Medicare payer perspective. Additionally, a 10-year lifetime horizon was evaluated to better understand the impact of long-term outcome uncertainty on cost-effectiveness. Based on recently published multicenter retrospective propensity score matched data, metastatic progression and survival probabilities were assumed to be equivalent between treatments. Utility values and additional probabilities, including both short and long-term treatment toxicities, were obtained from published literature. Primary outcomes of interest included effectiveness measured in quality adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICER) using a willingness-to-pay threshold of $100,000/QALY. One-way and probabilistic sensitivity analyses were performed to assess the robustness of the model. **Results:** At 5 years, the average cost was $32,286.35 higher for TMT versus RC. The average QALYs were 3.88 and 3.96 for RC and TMT respectively. TMT was not cost-effective at 5-year (ICER: $379,917.21/QALY) or 10-year (ICER: $222,704.78/QALY) time horizons. On one-way sensitivity analyses, TMT would become cost effective if: 1) TMT costs were less than $16,152; or 2) TMT resulted in a 13.3% improvement in metastasis free survival relative to RC. **Conclusions:** Although it resulted in similar quality and duration of life, TMT was not cost-effective relative to RC at 5 and 10 years given higher treatment costs. These findings support the role of both TMT and RC in management of MIBC and highlight the need for continued efforts to reduce healthcare costs associated with TMT. Research Sponsor: None.

Adherence to ASCO Language of Respect (LoR) guidelines in urothelial carcinoma (UC) abstracts at the 2023 ASCO Annual Meeting.

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Background: *The Language of Respect* (LoR) guidelines of ASCO were developed to promote patient-centered language and demonstrate the highest levels of respect and empathy when referring to people with cancer. In this study, we aimed to characterize the proportion of urothelial carcinoma (UC) abstracts from 2023 ASCO Annual Meeting that complied with these guidelines. **Methods:** AllpublishedUC abstracts from 2023 ASCO Annual Meeting were reviewed and validated for statements that complied with or deviated from the LoR guidelines by 6 reviewers. Collected statements were stratified into 3 groups in accordance with guideline recommendations: (1) Do not blame patients, (2) Respect the role of patients, (3) Do not dehumanize patients. Descriptive statistics were used to characterize compliance. Univariate and multivariate analyses were used to identify factors associated with non-compliance with the guidelines before and after adjustment for potential confounders such as presentation type, first author affiliation, and country of origin. **Results:** Overall, 120 abstracts were reviewed, of which 3 were excluded as they were basic science studies or lacked patient enrollment and did not include evaluable verbiage. 47.9%, 47.0%, and 5.1% of abstracts were accepted as online publication only, poster, and oral presentation, respectively. First authors were affiliated with institutions in native English-speaking countries (NESC) in 83 (70.9%) abstracts and non-native English-speaking countries (NNESC) in 34 (29.1%) abstracts. 75.2% of abstracts included authors from multiple institutions, and 70.1% included authors from a single country. 68.4% of abstracts contained at least one noncompliant statement, while 53.0%, 33.3%, and 0.9% had at least one statement that violated the "Do not dehumanize patients", "Do not blame", and "Respect the role of patients" guidelines, respectively. In univariate analysis, abstracts with authors from a single country and abstracts with first authors from NNESCs had greater odds of containing at least one statement noncompliant with the LoR guidelines (OR 2.93, 95%CI 1.27-6.73 [p=0.011] and OR 3.64, 95%CI 1.28-10.37 [p=0.016], respectively). Multivariate analysis showed that none of the assessed author characteristics were significantly predictive of noncompliant language. **Conclusions:** In this observational study, we found that a substantial proportion of UC abstracts failed to adhere to ASCO's LoR guidelines. Multilingual translations of the LoR guidelines, broader educational outreach, and attention to LoR adherence in the abstract review process may increase use of patient-respectful language at the ASCO Annual Meeting. Research Sponsor: None.

HER2 mutation and bladder cancer (BC): Prevalence and clinical outcomes.

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Background: Novel HER2-directed targeted therapies have revolutionized the treatment paradigm for patients with breast cancer and are being actively investigated in BC. The impact of pathogenic HER2 mutation and/or its amplification on clinical outcomes across various stages of BC is underdefined. **Methods:** In our retrospective study, we identified 999 BC patients who underwent genetic profiling using MSKCC IMPACT and had at least one year of follow-up. The BC disease states included non-muscle invasive (NMIBC), muscle-invasive (MIBC), and metastatic (MetBC). Patient demographics and HER2 alteration (mutation or amplification) were analyzed and compared closest to the time of IMPACT sampling, using the Kruskal-Wallis rank sum test or the Fisher's exact test. The Kaplan-Meier method was used to estimate overall survival (OS) and progression-free survival (PFS) for MIBC and MetBC, and advanced disease-free survival (ADFS) for NMIBC. The log-rank test and Cox proportional hazard regression were used in survival analyses. **Results:** The study cohort included NMIBC:359, MIBC:429, and MetBC:211 patients at the time of profiling and the overall incidence of HER2 alteration (mutation or amplification) was 13% (48), 17% (75), and 19% (41), respectively. HER2 Amplification was significantly lower for NMIBC (2.8%) compared to MIBC (9.3%) and MetBC (10%), $p<0.001$. HER2 S310F and S310Y were the most common pathogenic mutations. Age, race, gender, and smoking status were not associated with the incidence of HER2 alteration for any BC disease states. The median follow-up for NMIBC, MIBC, and MetBC was 5.3, 3.6, and 6.5 years, respectively. HER2 status did not influence ADFS for NMIBC; PFS and OS for MIBC regardless of neoadjuvant cisplatin chemotherapy (chemo); OS for 1st line (1L) MetBC treated with gemcitabine plus platinum (GC) chemo or 2nd line (2L) immune checkpoint inhibitor (ICI) therapy post 1L-chemo (table). **Conclusions:** We present one of the largest and comprehensive study of HER2 mutation in BC. Overall, HER2 amplification was significantly less frequent for NMIBC. HER2 alterations were not a prognostic marker for NMIBC or MIBC independent of neoadjuvant cisplatin-based chemo, MetBC- 1L GC-chemo and 2L ICI post GC-chemo. Further studies examining IHC and functional HER2 PET imaging are needed to further define the HER2 BC landscape. Research Sponsor: American Society of Clinical Oncology; MSKCC Support Grant/Core Grant.

	N (%)	Median ADFS (95% CI)	p Value
NMIBC			
Non-HER2-Altered	378 (88%)	13 (9.5, NA)	0.547
HER2 Altered	52 (12%)	9.6 (9.0, NA)	

	N (%)	Median PFS (95% CI)	p Value	N (%)	Median OS (95%CI)	p Value
MIBC						
Non-HER2-Altered	233 (83%)	2.7 (1.7, 4.0)	0.656	233 (83%)	5.3 (4.6, NA)	0.252
HER2 Altered	48 (17%)	3.0 (1.0, NA)		48 (17%)	8.4 (4.3, NA)	

	N (%)	1L-Chemo Median OS (95% CI)	p Value	N (%)	2L-ICI Median OS (95% CI)	p Value
MetBC*						
Non-HER2-Altered	111 (82%)	1.9 (1.4, 2.4)	0.443	49 (80%)	0.9 (0.6, 1.8)	0.498
HER2 Altered	25 (18%)	2.7 (1.6, 3.6)		12 (20%)	1.5 (0.7, NA)	

Estimating Bayesian priors for a non-inferiority randomized trial of gemcitabine-based chemoradiation for muscle invasive bladder cancer.

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Background: Gemcitabine (gem) is a convenient radiosensitizer for muscle invasive bladder cancer (MIBC). However, the effectiveness and toxicity of gem have not been studied in a randomized control trial (RCT) against non-gem radiosensitization. This analysis aims to generate informative Bayesian prior distributions for effectiveness and toxicity outcomes to be used in a non-inferiority RCT of gem versus non-gem radio-sensitizers. **Methods:** We extracted all patients (pts) treated with curative intent concurrent chemoradiotherapy for node negative MIBC at a single institution between 2010-2022 and divided into gem vs non-gem cohorts. To minimize impact of confounding, we used freedom from distant metastases (FFDM) as our primary measure of effectiveness, censoring for both loss to follow up and death. We used a non-informative uniform prior to estimate the posterior distribution of hazard ratios (HR) for FFDM. We used a non-informative Jeffrey's prior to estimate the posterior distribution of odds ratios (OR) for dichotomized acute grade 2 or higher gastrointestinal (G2+ GI) and genitourinary (G2+ GU) toxicities. We adjusted for age, T-stage, prior non-MIBC, neoadjuvant chemotherapy in all analyses. **Results:** A total of 106 pts were included (50 = gem, 56 = non-gem, of which 27 [48%] received mitomycin/5FU); 81% had cT2 disease and median radiation dose was 6480 cGy (range 4500-6480 cGy). Compared to pts in non-gem cohort, pts in gem cohort were older (mean age: 80 vs 76), had less advanced primaries (T3-T4: 14% vs 23%), were less likely to get neoadjuvant chemotherapy (12% vs 29%), were less likely to have prior non-MIBC (10% vs 13%), were less likely to complete full course radiotherapy (88% vs 94.6%), and had shorter follow-up (median 1.3 versus 2.3 years). The 2-year FFDM for the gem and non-gem were 62% and 66%. Table 1 shows rates of acute GI/GU toxicity. The median posterior HR (high probability density (HPD)) for FFDM was 1.54 (0.63-2.86). The OR (HPD) for grade 2+ GI toxicity was 2.4 (HPD 0.78-5.44) and grade 2+ GU toxicity was 0.91 (HPD 0.29-1.82) in gem vs non-gem cohorts. **Conclusions:** Our analysis suggests skeptical priors for FFDM (50% chance of at least 54% worse HR) and acute G2+ GI toxicity (50% chance of at least 140% worse OR) toxicity and a neutral prior for acute G2+ GU toxicity for a non-inferiority RCT of gem vs non-gem radiosensitization. Validation in a second institutional cohort will be available for our presentation. Research Sponsor: None.

	Gem (n=50)	Non-Gem (n=56)
GI		
G0	24%	32%
G1	40%	46%
G2	30%	20%
G3	6%	2%
GU		
G0	12%	11%
G1	46%	48%
G2	42%	36%
G3	0%	5%

Evaluation of provider preferences in first-line metastatic cisplatin-ineligible urothelial carcinoma in the setting of platinum shortages.

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Background: Standard of care for patients with metastatic urothelial carcinoma (mUC) who are ineligible to receive cisplatin has been gemcitabine and carboplatin (gem/carbo), and more recently followed by maintenance therapy with avelumab. Combination pembrolizumab (pembro) and the antibody-drug conjugate enfortumab vedotin (EV) has shown very promising results and is now approved for first-line therapy in cisplatin-ineligible patients based on the phase Ib/II EV-103 trial. We were interested in assessing providers' decision-making between gem/carbo and EV/pembro based on perceived comparative response rates and toxicity profiles, as well as the nationwide platinum chemotherapy shortage in 2023. **Methods:** We sent a 10-question encrypted electronic survey centered on a scenario of a mUC case to 150 oncologists via email listservs and social media. **Results:** We received 45 responses: 7 oncologists (15.6%) chose gem/carbo, 15 (33.3%) chose EV/pembro, and a majority, 23 (51.5%) chose to discuss both options with patients. 40 (88.9%) were academic or disease focused and 5 (11.1%) described their practice as general oncology. Of oncologists who chose gem/carbo, the most common reasons were: gem/carbo has more long-term data (86.6%) and lack of phase 3 data for EV/pembro (71.4%). Of oncologists who chose EV/pembro, the most common reasons were: higher response rates (86.7%) followed by the carboplatin shortage (40%). Only 6.7% chose the carboplatin shortage as the main reason while 73.3% chose higher response rates as the main reason. Of oncologists who chose to discuss both, the most common reasons why they would consider EV/pembro were: higher response rates (82.6%), followed by patient preference (56.5%), followed by the carboplatin shortage (43.5%). 60.9% chose higher response rates as the main reason why they would consider EV/pembro. **Conclusions:** This questionnaire-based study of predominantly academic genitourinary oncologists suggests that the majority would consider EV/pembro as a first-line treatment for cisplatin-ineligible patients with mUC. The primary reason for this choice was the belief that it has higher response rates, as opposed to the national shortage of carboplatin or concerns regarding toxicity. We anticipate that the awaited results of the EV-302 trial in the coming months will also change the treatment landscape of mUC. However, similar issues may be relevant in the future for other treatment decisions in which incomplete information is available or with ongoing chemotherapy shortages. Research Sponsor: None.

Outcomes with neoadjuvant chemotherapy in bladder-preserving treatment for MIBC.

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Background: Trimodality bladder preservation is an acceptable alternative to radical cystectomy (RC) for muscle invasive bladder cancer (MIBC). Multiple retrospective studies have reported similar disease control rates and overall survival rates with chemoradiation (CRT), but the benefit of neoadjuvant chemotherapy (NAC) prior to CRT is not established. This study investigates the outcomes of CRT with or without NAC for management of MIBC. **Methods:** Retrospective analysis of 135 adult patients with muscle invasive bladder cancer evaluated in the Department of Radiation Oncology over 7 years (2016-2022). Patients were excluded if they did not receive NAC or if they underwent RC. Patients were treated with NAC followed by CRT. Overall survival (OS), progression-free survival (PFS), and metastasis-free survival (MFS) were calculated using Kaplan-Meier methods. Follow-up was censored at 36 months after treatment. Differences in survival outcomes by completion of status of NAC were analyzed using log-rank tests. All survival analyses were performed in SAS version 9.4. **Results:** Of the 135 evaluated patients, 38 were treated with NAC followed by CRT. The 24-month OS, PFS, and MFS were 76% [95% CI 62-92%], 60% [95% CI 46-79%], and 72% [95% CI 58-90%] respectively. The 24-month PFS in patients who received a full course of NAC was 66.0% [95% CI 50-87%]) and 38.0% [95 CI 15-92%] in those who did not complete NAC regimen. Overall PFS was significantly higher in the NAC cohort (log-rank p=0.03). There was no significant difference in OS between patients who completed prescribed course of NAC versus those who did not (log-rank p=0.48). Treatment was overall well tolerated with 28.2% of grade 2 or higher RT toxicity. **Conclusions:** NAC prior to CRT achieved excellent short term disease-free and survival outcomes in patients with non-metastatic MIBC. This analysis is limited by its retrospective nature but suggests that completion of NAC prior to CRT may be associated with lower rates of disease recurrence. Research Sponsor: None.

Patient and tumor characteristics.

Characteristics	Overall N (%) or median (IQR)	Full NAC N (%) or median (IQR)	No Full NAC N (%) or median (IQR)	p-value
	N=38	N=29	N=9	
Age (range), years	73.9 (65.1-77.8)	73.5 (64.10, 77.49)	74.84 [73.17, 77.86]	0.53
Gender				
Female	3 (7.9)	2 (6.9)	1 (11.1)	>0.99
Male	35 (92.1)	27 (93.1)	8 (88.9)	
Race				
Asian	4 (10.8)	4 (14.3)	0 (0.0)	0.48
White	4 (10.8)	3 (10.7)	1 (11.1)	
Other	29 (78.4)	21 (75.0)	8 (88.9)	
Ethnicity				
Hispanic	2 (5.4)	1 (3.6)	1 (11.1)	0.98
Non Hispanic	35 (94.6)	27 (96.4)	8 (88.9)	
Smoking status				
Current	4 (10.5)	1 (3.4)	3 (33.3)	0.03
Former	17 (44.7)	15 (51.7)	2 (22.2)	
Never	17 (44.7)	13 (44.8)	4 (44.4)	
Stage				
T1	3 (7.9)	2 (6.9)	1 (11.1)	0.31
T2a	24 (63.2)	20 (69.0)	4 (44.4)	
T2b	9 (23.7)	5 (17.2)	4 (44.4)	
T3b	2 (5.3)	2 (6.9)	0 (0.0)	
Histology				
Small cell carcinoma	2 (5.3)	2 (6.9)	0 0.0)	0.15
SCC	1 (2.6)	0 (0.0)	1 (11.1)	
Urothelial/transitional cell	35 (92.1)	27 (93.1)	8 (88.9)	

Development of a novel machine learning-based predictive risk calculator for radical cystectomy.

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Background: Radical cystectomy (RC) is a standard treatment for patients with muscle invasive and certain high-risk non-invasive bladder cancers. Existing clinical risk calculators based for RC on standard regression methods have demonstrated poor, inaccurate predictions of post-operative risks and adverse outcomes. We aimed to build a risk calculator using novel machine learning methods to predict complication rates and other outcomes based on clinical characteristics of patients undergoing RC. **Methods:** Patients who had an RC for bladder cancer between 2019 and 2021 were pulled from the National Surgical Quality Improvement Database. Potential predictors included clinically meaningful characteristics such as patient demographics, pre-operative labs, comorbidities, pre-operative bowel and antibiotic preparations, and prior treatment history, as well as cystectomy-specific characteristics such as diversion type and surgical approach. Outcomes included risk of any complication, infectious complication, mortality, and readmissions. Logistic regression, random forest, and support vector machine algorithms were used to build predictive models. Models were optimized assessed with area under the ROC curve (AUROC) and average precision (AP). **Results:** 8,936 patients were included in the sample dataset. Random forest classifiers outperformed other models for predicting risk of any complication (AUROC = 0.662; AP = 0.66), infectious complication (AUROC = 0.615; AP = 0.20), and mortality (AUROC = 0.603; AP = 0.03). The logistic regression model best predicted readmissions (AUROC = 0.587; AP = 0.26). Top predictors of complication risk included operation time, glomerular filtration rate, and type of procedure (robotic vs. open). Infectious complication was best predicted by wound classification and diversion type, mortality was best predicted by BMI and operation time, and readmissions was predicted most by pre-existing renal failure and emergent cases. **Conclusions:** Machine learning-based risk calculators were more effective in predicting morbidity and mortality after RC compared to more standard predictive algorithms. Machine learning algorithms therefore demonstrate greater predictive potential when given a wide range of clinical characteristics. Research Sponsor: None.

Outcome	Best Model	AUROC	Avg. Precision	Top Predictors
Any Complication	Random Forest	0.662	0.66	Op Time, GFR, BMI, Surg. Approach
Infectious Complication	Random Forest	0.615	0.22	ASA Wound Class, Diversion Type, Op Time, GFR, Race
Mortality	Random Forest	0.603	0.03	BMI, Op Time, GFR, Age
Readmission within 30 Days	Logistic Regression	0.587	0.26	Renal Failure, Emergent Case, Weight Loss, Diversion Type

Unraveling the web of frailty: A novel approach to frailty using a CGA-derived spider plot.

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Background: Frailty in bladder cancer predicts increased complications and mortality. Measuring frailty is challenging because relying on one frailty instrument risks oversimplifying patients' multidimensional vulnerability profiles. Current guidelines recommend using a comprehensive geriatric assessment (CGA) to quantify frailty across domains of physical function, mental health/cognition, nutrition, and multimorbidity in older adults. However, the CGA's extensive data can be hard to synthesize and integrate into busy clinical practice. We propose a novel CGA-derived Frailty Spider Plot, synthesizing CGA-identified vulnerabilities into a clinically useful frailty profile. **Methods:** Urothelial cancer patients, prospectively enrolled between 9/2020 and 7/2021 in a multidisciplinary bladder cancer clinic, completed a CGA incorporating validated assessments of functional status, multimorbidity, nutrition, cognition, and mental health, augmented with CT-derived assessments of muscle mass and adiposity. Spearman Correlation Coefficients were used to quantify relationships between frailty tools and domains. Novel Frailty Spider plots were then created to visualize individuals' distinct frailty phenotypes. The CGA instruments, grouped by domain, were the spokes of the plot, with each node determined by validated thresholds. Outer ring values indicated greater frailty. **Results:** The cohort included 67 patients (median age 71, 16.4% female), most with muscle-invasive bladder cancer (77.6%; cN+: 20.9%, M1: 7.6%). The CGA identified 31.4% vulnerable-to-moderately frail, 23.9% at risk for falls, 13.4% with mild depression, 7.5% with moderate-severe depression, 3% with mild/moderate dementia, 34% at risk for malnutrition, and 6% malnourished. Frailty measures were generally weakly correlated (rho $<|0.5|$). Individuals' specific risk profiles were plotted on the novel Frailty spider plot which visually distinguished patients according to their frailty phenotypes. For instance, a patient with a high risk Mini-nutritional Assessment score, hypoalbuminema, and sarcopenic skeletal muscle mass, is distinguished with a Spider plot dominated by nutritional frailty spokes. **Conclusions:** In this prospective observational cohort, a CGA identified key vulnerabilities beyond a standard risk assessment. Frailty domains provide unique risk insights beyond relying on simple frail/not frail nomenclature. Notably, even within a domain, instruments had low correlations, contributing distinct insights into a patient's vulnerability profile. Our novel Spider plot approach visually synthesizes this data in a single depiction of the predominant components of frailty that can be targeted by personalized prehabilitation interventions. Future work will refine risk assessment instruments to best predict clinical outcomes, creating parsimonious Frailty spider plots for clinical use. Research Sponsor: BCAN.

Analysis of a national database to evaluate place-of-death preferences among patients with bladder cancer in the United States of America from 2003 to 2020.

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Background: Bladder Cancer (BC) is associated with significant treatment related morbidity and mortality risk. End of life care (EOL) and advance care planning are crucial in oncology care of BC patients. Place of Death (PoD) is an important determinant of patient and caregiver preference, access to home-based supportive care, and cost of caregiving at EOL. We evaluate trends in PoD for patients and hospice utilization with BC in the U.S. from 2003 to 2020 based on the CDC WONDER (Centers for Disease Control and Prevention for Wide-ranging Online Data for Epidemiologic Research) database. **Methods:** We analyzed data using the CDC WONDER database from January 01, 2003, to December 31, 2020. The data for deaths due to bladder cancer was pooled using the International Classification of Diseases-10th (ICD-10) Revision code as C67, C67.1, C67.2, C67.3, C67.4, C67.5, C67.8, C67.9. The inclusion criteria included patients aged >18. The demographic data was obtained to calculate descriptive statistics using age, gender, PoD, census region, and utilization of hospice mortality accordingly over the past two decades. **Results:** The analysis demonstrated that overall mortality due to BC were 319,229 from 2003-2020. Of these deaths, 27,990 (8.8%) were recorded in hospice facilities. The hospice mortality has steadily increased from 0.3% in 2003 to the highest of 9.10% in 2019, with a sharp decline to 7.3% in 2020. We noticed the PoD differed based on racial subgroups. More than half of African American (AA) population mortality was observed in a medical facility (57.01%) compared to Whites (50.27%). Hospice or death at home in AA were (42.99%) compared to whites (49.73%). Age stratified mortality analysis showed decreased hospice utilization in 25-44 yrs (9.61%) vs 65+ yrs (10.15%). Stratifying the results by the state census showed highest hospice utilization in Florida (25.23%) vs the lowest in Virginia (2.51%). **Conclusions:** To our knowledge this is the first study utilizing CDC WONDER database to demonstrate PoD preferences in BC related deaths. We observed a steady increase in hospice utilization from 2003-2020 throughout the US with a decline in 2020 possibly related to COVID pandemic. AA had higher mortality in medical facilities compared to whites, whereas the white population has utilized more hospice services or died at home. This study highlights the need for further efforts and policy changes needed to improve hospice utilization across the US with a focus on improved access to EOL care in BC patients. Research Sponsor: None.

Avelumab first-line maintenance (1LM) for advanced urothelial carcinoma (aUC): Long-term patient-reported outcomes (PROs) in the phase 3 JAVELIN Bladder 100 trial.

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Background: In the JAVELIN Bladder 100 trial, avelumab 1LM + best supportive care (BSC) significantly prolonged overall survival vs BSC alone in patients (pts) with aUC that had not progressed with 1L platinum-based induction chemotherapy, and health-related quality of life was maintained. We report long-term and exploratory PRO analyses in the overall avelumab + BSC arm (any treatment duration) and in the subgroup with ≥12 months of avelumab treatment. **Methods:** In JAVELIN Bladder 100 (NCT02603432), PROs were a secondary endpoint assessed at baseline, on day 1 of each 4-week cycle, at end of treatment/withdrawal, and up to 90 days post treatment. PRO instruments used were National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Bladder Symptom Index-18 (FBlSI-18) and EuroQol 5 Dimensions 5 Levels (EQ-5D-5L). Descriptive and mixed-effect model analyses were conducted. Data were not evaluated in the BSC alone arm because few pts remained on study treatment at later time points. **Results:** At data cutoff (Jun 4, 2021), median follow-up in the avelumab arm (n=350) was 38.0 months (≥2 years in all pts), and median duration of treatment was 5.8 months. In pts treated for ≥12 months (n=118 [33.7%]), baseline characteristics were similar to those in the overall avelumab + BSC arm, except for a higher proportion with ECOG performance status of 0 (70.3% vs 60.9%) and lower proportion with visceral metastases (47.5% vs 54.6%). In both populations, completion rates for both PRO instruments among evaluable pts were >80% at all time points during treatment. On average, PRO scores remained stable throughout treatment, and no clinically relevant changes from baseline were reported (Table). Among pts treated for ≥12 months, ≈75% of evaluable pts reported no change or a decrease in being bothered by treatment side effects throughout 24 months of treatment. **Conclusions:** Prolonged avelumab 1LM treatment (≥12 months) was associated with stable PROs, indicating preservation in quality of life. The results further support the use of avelumab 1LM until progression or unacceptable toxicity as standard of care with level 1 evidence in pts with aUC who are progression-free after platinum-based chemotherapy. Clinical trial information: NCT02603432. Research Sponsor: This study was sponsored by Pfizer and was previously conducted under an alliance between the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945) and Pfizer; This analysis was sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany.

	Least-squares Mean Change From Baseline (95% CI)	
	Overall Avelumab + BSC Arm (n=350)	Pts with ≥12 Months of Avelumab Treatment (n=118)
FBISI-18 total score	−2.15 (−3.25, −1.04)	1.28 (0.08, 2.49)
Disease related symptoms–physical	−1.39 (−1.88, −0.89)	−0.05 (−0.63, 0.52)
Disease related symptoms–emotional	0.27 (0.11, 0.44)	0.68 (0.46, 0.91)
Treatment side effects	−0.42 (−0.73, −0.11)	0.22 (−0.16, 0.59)
Function/well-being	−0.15 (−0.34, 0.04)	0.36 (0.09, 0.62)
EQ-5D-5L index score	−0.07 (−0.09, −0.05)	−0.02 (−0.04, 0.00)
Visual analog scale	−1.14 (−2.95, 0.67)	4.16 (2.09, 6.23)

Treatment patterns and outcomes by age in metastatic urothelial carcinoma (mUC): A retrospective tertiary cancer center analysis.

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Background: Older adults with locally advanced or mUC often do not receive optimal first-line (1L) therapy (Rx) and subsequent treatments (Lara et al. ASCO 2016). There are limited randomized data for age-appropriate Rx in older mUC adults. Through our real-world study, we describe the clinical characteristics, treatment patterns, and outcomes among pts with mUC, comparing older to younger adults receiving 1L systemic Rx. **Methods:** This retrospective IRB-approved study included pts receiving care between 2014 and 2023 at the University of Utah, Huntsman Cancer Institute, a tertiary care National Cancer Institute-Designated Comprehensive Cancer Center. Eligible pts had a confirmed diagnosis of mUC and received 1L chemotherapy or 1L immunotherapy-based regimens. Based on age at receipt of 1L Rx, pts aged 70 years or above were grouped in the 'older' group, while rest were included in the 'younger' cohort. Survival and Rx-related outcomes of those enrolled inwere excluded. Overall survival (OS) between the two groups was compared using Kaplan-Meier and Cox Regression analysis. All statistical analyses were implemented in R-Studio (v.4.2). **Results:** We identified 212 eligible mUC pts (103 older vs. 109 younger). Older pts received more immunotherapy-based Rx in the 1L (52.4% vs 35.7%, p=0.02), were more likely to be (73.6% vs. 45.4%, p<0.001), less likely to receive subsequent lines of Rx (median; range: 0 (0-3) vs 1 (0-5), p=0.005) and had lower clinical trial participation (69.9% vs 81.6%, p=0.04)compared to younger pts. For survival outcomes and treatment-related analysis, 160 patients (72 older vs. 88 younger) undergoing approved standard of care were included. Among mUC treated with 1L chemotherapy (n=108), more pts required dose adjustments in older group (23/43 vs 15/65 younger). Older adults received less number of cycles of chemotherapy (median; range: 4 (0-6) vs 5 (1-12), p= 0.03). Older pts had OS comparable to younger pts (11.2 mos vs. 14 mos, p=0.06). Pts from both age groups had similar rates of Rx-related toxicity and healthcare visits, independent of the type of systemic Rx. **Conclusions:** Older pts with mUC tend to be cis-ineligible and have lower bone marrow reserve. Nevertheless, select pts can be treated with risk-adjusted regimens of chemotherapy and with immunotherapy with comparable outcomes to younger mUC pts in terms of toxicity and outcomes. Validated tools to predict vulnerabilities and excessive chemotherapy-related toxicity in older adults with mUC are available and may help mitigate toxicity by informing Rx adjustments. Research Sponsor: None.

20-year trends in perioperative outcomes in patients with bladder cancer undergoing radical cystectomy with ileal conduit urinary diversion.

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Background: Radical cystectomy is associated with considerable postoperative morbidities. Enhanced recovery after surgery protocol is a multimodal perioperative pathway implemented to improve post-surgical outcomes over the past decade. We sought to compare the 30- and 90-day postoperative morbidity and mortality rates following RC and ileal conduit urinary diversion between 2000-2010 and 2010-2020 to evaluate the trends in patient outcomes and areas that need improvement. **Methods:** This retrospective cohort study used data from TriNetX US Collaborative network which allowed access to de-identified patient health records from over 43 healthcare organizations. ICD-10 codes were used to identify patients with bladder cancer who underwent radical cystectomy and ileal conduit urinary diversion from 01/01/2000 to 01/01/2020. The rates of 30 and 90-day postoperative morbidities and mortalities were compared between 2000 – 2010 and 2010 – 2020 using the chi-squared test. **Results:** The 30 and 90-day complications by decade were summarized in Table. There were 738 cases reported from 22 HCOs from 2000 to 2010 and 10,052 cases reported from 43 HCOs from 2010 to 2020. The overall all-cause mortality at 30 and 90-days postop were 1.5% and 4.4%, respectively, and remain unchanged over the past 20 years. The most common complications within 90-days postop were urosepsis (19.1%), acute kidney injury (16.3%), and UTI (15.6%). While most complication rates remain stable, the rates of urosepsis, acute kidney injury, and UTI were higher between 2010 to 2020 compared to 2000 to 2010. **Conclusions:** Radical cystectomy and urinary diversion procedure is associated with high perioperative morbidities with up to 1 in 5 patients experiencing a complication within 90-days postop. Despite reported improvement in cancer-specific survivals from recent reports, the overall morbidity and mortality rates associated with the procedure have not improved over the past two decades. Further research is needed to improve surgical outcomes, especially in infectious complication and renal function, for patients with bladder cancer undergoing radical cystectomy. Research Sponsor: None.

Radical Cystectomy Complication Rates	Total cohort* N = 10,740	Years 2000-2010 N = 738	Years 2010-2020 N = 10,052
30-day Urosepsis Complication (%)	11.9%	9.5%	12.1%
30-day Renal Failure Complication (%)	11.7%	5.7%	12.1%
30-day UTI Complication (%)	9.0%	6.9%	9.1%
90-day Urosepsis Complication (%)	19.1%	16.1%	19.3%
90-day Renal Failure Complication (%)	16.3%	11.0%	16.7%
90-day UTI Complication (%)	15.6%	14.0%	15.7%
All-Cause Mortality at 30-days (%)	1.5%	1.4%	1.5%
All-Cause Mortality at 90-days (%)	4.4%	4.7%	4.4%

*Discrepancy due to timeline limitations and cohort size in TriNetX dataset.

Real world outcomes for maintenance avelumab treatment in locally advanced/ metastatic urothelial cancer after platinum-based chemotherapy.

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Background: Maintenance Avelumab after platinum-based chemotherapy in metastatic-/ locally advanced urothelial carcinoma has shown overall and progression free survival benefit in the JAVELIN Bladder 100 trial. We analysed real world outcomes from 6 UK centres. **Methods:** Retrospective electronic patient records review was carried out for patients treated between January 2021 and September 2023 at 6 UK centres. Patients whose disease had not progressed after platinum-based chemotherapy were started on maintenance avelumab 800mg given at 2 weekly intervals, starting within 12 weeks of last day of chemotherapy as per the National Cancer Drug Fund criteria. Survival outcomes were established using the Kaplan Meier method and compared by a log rank test using SPSS. **Results:** In total 80 patients (median age 73 years-range 21-86) were included of which 68% were male and 32% were female. 31(38.8%) had prior upper tract and 49(61.2%) had bladder cancers. Metastases were in the nodes only in 33(41.5%) patients whilst 16.9% and 42.3% had bone and visceral metastases respectively. The number of patients with ECOG PS 0,1 and 2 were 36 (45.0%), 33 (41.3%), and 10 (12.5%), respectively. After a median of six cycles of platinum-based chemotherapy, 11.3% had a complete response, and 54.9% had a partial response. Patients then proceeded to maintenance avelumab treatment. Before treatment, the median Neutrophil to Lymphocyte Ratio (NLR) was 2.89. The number of patients with NLR $\leq$2.89 was 37 (46.3%), and with $>$2.89 were 38 (47.9%). Median number of cycles were 9 (range 1-66). At a median follow-up of 16.7 months, the median PFS was 8.3 months (95% CI 4.8-15.4). At the data cut-off, 37 patients had died, and 40 patients had progressed. Any grade of adverse event occurred in 34 (42.5%) patients. Grade 3 or higher toxicity rate was 7.5%. Two grade 3 allergic reactions were seen. One patient had Grade 3 immune mediated hepatitis and one patient had grade 3 immune mediated arthritis. Two grade 2 immune mediated colitis were reported. The ORR of avelumab maintenance therapy was 12.5%. 2 patients had a complete response, 8 had a partial response, and 43(53.7%) had stable disease. Within the limit of our small data set, univariate analysis for PFS revealed that there was no significant association between PFS and visceral metastases (p=0.2), bone metastases (p=0.2), node only metastases (p=0.6), primary site(p=0.9), and ECOG PS (p=0.6). However, NLR was a significant prognostic factor for PFS. The median PFS in patients with NLR $\leq$2.89 vs $>$2.89 was 16.9 vs 4.2 months, respectively (p=0.001). **Conclusions:** Our multi centre UK real world data confirms that maintenance Avelumab treatment is well tolerated, and its efficacy data is consistent with previously reported clinical studies. Research Sponsor: None.

Characterizing psychological resources and resilience in patients with bladder cancer: Associations with frailty and quality of life.

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Background: Bladder cancer (BC) profoundly affects patients' mental and physical well-being, with significant impacts to quality of life (QOL), mental health, and ability to perform activities of daily living. Understanding factors that influence patients' responses to BC is crucial to tailored care. One such factor that has yet to be studied in BC patients is resilience, or the ability to maintain or restore baseline function following a stressor. Our objective was to demonstrate the feasibility of prospectively characterizing baseline resilience and frailty in patients with BC. We hypothesized that resilience and psychological resources (PsyResources) would be positively associated with improved QOL and inversely associated with frailty. **Methods:** With IRB approval, we enrolled patients with BC (N=67) from a urology clinic (6/20-7/2021). Patients completed a comprehensive geriatric assessment incorporating validated assessments of frailty and PsyResources: University of Washington Resilience Survey (UWR), Psychological Capital (PsyCap), Brief Inventory of Thriving (BIT), and Self-Compassion Survey (SCS) which measure resilience, psychological capital, mental health, and self-compassion, respectively. Validated QOL surveys were completed at 2 weeks, 3 and 6 months post-treatment. Correlation matrices evaluated PsyResources' links with baseline frailty and Spearman's correlation coefficient (ρ) was reported. Associations between PsyResources, anxiety and depression, and QOL were evaluated with linear regression. **Results:** The median age of the cohort was 71 (83.6% male) and 77.6% had muscle-invasive BC (cN+:20.9%, M1: 7.6%). PsyResource assessment completion rates ranged 96-100% and had strong inter-assessment associations (ρ=0.52-0.81, $p< 0.0001$ for all). Baseline PsyResources were strongly inversely correlated with the geriatric depression scale, (ρ=-0.50-0.65, $p<0.0001$). Negative correlations were found between functional frailty and SCS (ρ=-0.37, p=0.006). A higher baseline of each PsyResource was associated with improved global symptoms, emotional function, and body image (BIT and SCS) ($p<0.05$) and decreased anxiety and depression over time (B:-0.167 to -2.46; $p<0.02$). **Conclusions:** We present the first prospective characterization of baseline PsyResources in patients with BC, revealing positive correlations with mental health and inverse correlations with functional frailty. Interestingly, PsyResources were associated with improved QOL outcomes over time. Ongoing work is exploring the relationship between resilience and different domains of frailty and the potential role of functional recovery and decline following BC treatment. Future work will also evaluate associations with survival outcomes and the ability to modify resilience to facilitate recovery of functional status and quality of life after treatment. Research Sponsor: Bladder Cancer Advocacy Network.

Thromboembolic events associated with neoadjuvant chemotherapy for muscle invasive cancer of the bladder.

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Background: Patients with muscle invasive bladder cancer who undergo platinum-based neoadjuvant chemotherapy (NAC) followed by radical cystectomy or radiotherapy are at high risk of venous and arterial thromboembolic events (TEE). TEE is associated with delay to radical cancer treatment, significant morbidity and even mortality. This study aimed to document the incidence and characteristics of TEE during NAC and prior to radical treatment. **Methods:** Retrospective data was collected on all patients in our centre who underwent NAC prior to radical treatment. TEE events were identified based on routine imaging to assess for response to NAC; or imaging based on clinical symptoms developed during (or within 28 days) of NAC but prior to radical treatment. **Results:** Data was collected on 148 patients between January 2015 and September 2023. Age range: 44 - 82 years, the majority (73.6%) of whom were male. All patients received platinum-based chemotherapy (median 4 cycles). A total of 31 patients (20.9%) developed 35 TEE, including 27 venous events (24 pulmonary emboli and 3 deep venous thromboses), and 8 arterial events (3 aortic thrombus, 4 limb ischaemia, 1 ischemic stroke). Four patients had a venous and arterial TEE. The majority of pulmonary venous TEE were subclinical. **Conclusions:** Our single-centre study demonstrates that the incidence of TEE during NAC prior to radical treatment for bladder cancer is high. Improved imaging techniques and routine scans post-NAC led to identification of subclinical TEE that require treatment as they are likely to become clinically significant. The high rate of TEE in this patient population is likely to benefit from prophylactic anticoagulation during NAC and should be investigated in future prospective clinical trials. Research Sponsor: None.

De novo financial toxicity following radical cystectomy for bladder cancer and its impact on health-related quality of life.

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Background: Financial toxicity (FT) is a patient-reported outcome measure (PROM), defined as the detrimental effect of financial burden caused by a cancer diagnosis on a patient's well-being. Although FT is common among cancer patients, little is known about FT following radical cystectomy for bladder cancer in countries with universal health coverage. We aimed to assess de novo FT and its impact on health-related quality of life (HRQOL) in a large prospective cohort of patients undergoing RC with a systematic follow-up of up to 10 yrs. **Methods:** 1606 consecutive patients who underwent RC at a large tertiary care center were included. PROMs were prospectively assessed preoperatively, postoperatively at 3mo, then annually until a maximum follow-up of 120mo, applying the validated EORTC QLQ-C30 questionnaire, and the bladder cancer-specific QLQ-BLM30 and FACT-BL-questionnaires. FT was assessed by the "financial toxicity subscale" (FTS) of the EORTC QLQ-C30. Based on previous reports, meaningful FT was defined as FTS $\geq$ 17. Multivariable regression analysis was used to identify predictors for the development of de novo FT. Separate modeling of longitudinal HRQOL was performed for patients with de novo FT (FT-cohort) and without FT (no-FT-cohort). **Results:** 93 Patients reporting FT prior RC were excluded from further analysis. 37.6% of the included patients reported de novo FT within 12 months after RC with a mean FTS-score of 55.2 (SD 26.3). Baseline clinicopathological characteristics did not differ between the FT-cohort and the no-FT-cohort (p-range .072-.370). Multivariable logistic regression analysis revealed male gender (OR 3.448, 95%CI 1.10-11.49, p=.045), urban neighborhood (OR 1.532, 95%CI 1.01-2.53, p=.049), a positive smoking history (OR 2.491, 95%CI 1.18-5.26, p=.017) and ileal conduit urinary diversion (OR 2.179, 95%CI 1.03-4.61, p=.042), to independently predict de novo FT following RC. Longitudinal analysis of HRQOL revealed no significant difference in baseline general HRQOL assessed by the global health status domain (GHS) between both cohorts (p=.934). Postoperatively, patients with de novo FT reported significantly worse general HRQOL compared to patients without FT (p= .001). In the longer term, the FT-cohort reported significantly worse GHS scorer up to 84mo after RC. **Conclusions:** The current study provides prospective data from a unique contemporary patient cohort, which reveals independent predictors for de novo FT following RC. Furthermore, it displays the natural course of general HRQOL for patients who develop de novo FT. Research Sponsor: None.

Adverse effects and discontinuation of pembrolizumab in BCG refractory non-muscle invasive bladder cancer.

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Background: Non-muscle invasive bladder cancer (NMIBC) is associated with high rates of recurrence and progression despite adequate intravesical treatment with Bacillus Calmette-Guerin (BCG). Pembrolizumab was found to be effective in treating BCG-refractory NMIBC in the KEYNOTE-057 trial with a 41% complete response after 3 months and minimal adverse effects. As a result it was approved by the FDA on January, 2020, for the treatment of high risk BCG-unresponsive NMIBC with carcinoma in situ (CIS) with or without papillary tumors in patients ineligible for or unwilling to undergo cystectomy. This study reports a single institution's experience using pembrolizumab in BCG refractory patients with high-risk NMIBC.
Methods: Records of NMIBC patients who commenced treatment with pembrolizumab between January 2020 and January 2023 at a single institution were retrospectively reviewed. Demographic and clinicopathologic information was collected. Kaplan-Meier curves were generated to calculate progression-free survival (PFS), and treatment-specific survival (TSS). The combined positive score (CPS) of PD-L1 was assessed for each case treated by pembrolizumab.
Results: Out of 250 patients with NMIBC who were screened for the study, 18 met the inclusion criteria. The median age was 74.1 years (IQR=67.8 – 81.4), male to female ratio of 3.5:1. The median follow-up time was 17.5 months (IQR= 8.1–22.5). A previous history of CIS was present in all patients as well as second-line chemotherapy for BCG refractory disease. At the start of pembrolizumab, stage distribution was as follows: 1 (5.6%) cTa, 6 (33.3%) had CIS, and 11 (61.1%) cT1. After an average of 8.9 cycles, 72.2% (13/18) stopped treatment. 27.8% (5/18) are still undergoing treatment, with an average of 12.6 cycles (SD=10.4). 1 out of the 13 patients who stopped treatment had a complete response. The remaining reasons for termination of treatment are Grade 2 or higher immune-related adverse events in 53.8% (7/13), progression in 30.8% (4/13), and recurrence in 7.7% (1/13). Four patients ultimately required radical cystectomy which revealed 1 pTa, 1 pTis, 1 pT1, and 1 pT4. Only 1 patient had CPS of PD-L1 $>$ 10.
Conclusions: There were higher rates of toxicity from pembrolizumab for the treatment of BCG-refractory NMIBC than expected. More research is needed to better define the patients who are likely to benefit from this treatment. Pembrolizumab for BCG refractory NMIBC can have high rates of Grade 2 or higher adverse events leading to early withdrawal from treatment. Early discussion about radical surgery remains an important part of the treatment guidelines for BCG refractory NMIBC. Research Sponsor: None.

Clinical outcomes with split-dose cisplatin-based regimens in patients (pts) with locally advanced or metastatic urothelial carcinoma (la/mUC): Results of a systematic literature review (SLR) and network meta-analysis (NMA).

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Background: Gemcitabine + cisplatin (GC) is one of the most effective and commonly used regimens in la/mUC. In GC, cisplatin is dosed at 70 mg/m^2 on day 1 of a 3-week cycle; however, for many pts, impaired renal or cardiac function, neuropathy, or poor performance status can preclude use of cisplatin. A promising alternative is split-dose GC, where the cisplatin dose is divided over 2 days. We conducted an SLR and NMA to better understand outcomes, toxicity, and comparative effectiveness of split-dose GC vs GC, GCarboplatin (GCa), and methotrexate + vinblastine + doxorubicin + cisplatin (MVAC). **Methods:** An SLR, performed on March 8, 2023, followed Cochrane guidelines to identify observational studies of treated pts with la/mUC and randomized and nonrandomized trials investigating split-dose cisplatin regimens for this indication. *No limits were placed on publication year or geography, and* studies reported in English, Spanish, French, and German were included. An NMA was conducted for objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). Results were reported as odds ratios or hazard ratios (HRs) with 95% credible intervals (Crls). **Results:** Among 120 studies that met SLR inclusion criteria, 16 (6 clinical trials, 10 retrospective studies) conducted in the US, Europe, and Asia published from 1999-2023, representing 1,767 pts, included split-dose GC. Common reasons for choosing split-dose GC were impaired renal function (creatinine clearance ≤60 mL/min), age >70 years, comorbidities, and physician preference. Most often, cisplatin was split (35 mg/m^2) on days 1+8 or 1+2, and pts received a median of 3-5 cycles. In studies reporting outcomes with split-dose GC (12 studies), ORRs were 39-80% (11 studies), median PFS was 3.5-9.9 months (7 studies), and median OS was 8.5-18.1 months (11 studies). Discontinuation rates due to adverse events were 8-38% (5 studies). In the NMA, ORR for split-dose GC was significantly higher than GCa but not GC and MVAC. PFS and OS for split-dose GC were not significantly different from GCa, GC, or MVAC (Table). **Conclusions:** This is the first SLR and NMA of split-dose GC in la/mUC. Despite heterogeneity in the limited studies included, survival with split-dose GC was numerically better than GC and worse versus MVAC but not statistically different in either case. Split-dose GC has the potential to extend the la/mUC population eligible to receive cisplatin-based regimens and warrants further study. Research Sponsor: The study was sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

Split-dose GC vs intervention	ORR odds ratio (95% Crl)	PFS HR (95% Crl)	OS HR (95% Crl)
GC	1.12 (0.74-1.70)	0.86 (0.14-4.23)	0.91 (0.56-1.47)
MVAC	0.93 (0.32-2.61)	1.09 (0.06-16.19)	1.46 (0.74-2.97)
GCa	1.97* (1.29-3.02)	0.77 (0.12-3.90)	0.80 (0.48-1.36)

Odds ratio >1 favors split-dose GC, HR <1 favors split-dose GC. * = significant.

Analysis of therapy attrition and changes in outcomes over time for patients (pts) with advanced urothelial cancer (aUC) treated at an academic center.

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Background: Despite recent advances in treatment (Tx) options for pts with aUC, real world data suggest that <50% of pts starting Tx receive 2nd line Tx and <15% receive 3rd line Tx. We hypothesized that aUC pts treated at an academic center would have lower Tx attrition rates which would translate into improved outcomes for pts treated more recently. **Methods:** We identified pts with aUC treated since 2011 and analyzed pts who received systemic Tx for metastatic disease, including baseline characteristics, Tx lines and outcomes. Date of 1/1/2019 for Tx start was used to divide pts into earlier vs later Tx groups. Overall survival (OS) from Tx start was assessed using Kaplan Meier Method in pts who started Tx >1 year before censor date of 12/31/2022 for survival. Chi-square test and Wilcoxon rank sum test were used to compare proportions and numerical data, respectively. **Results:** Among 360 pts with aUC, 237 received 1st line Tx from 09/2011-08/2022. Of 237 pts, 133 (56%) received 2nd line Tx, 61 (26%) 3rd line Tx, 30 (13%) 4th line Tx, and 10 (4%) > 4 Tx. Pts with Tx in the later group (start after 1/2019) had higher ORR with 1st and 2nd line Tx (Table) and more NGS testing (87% vs 54%, p<0.001) relative to earlier group. With median follow-up of 29.5 mos, median OS was 24.2 mos (95% CI: 17.4 – 29.7) for all pts. Pts in the later group (Tx started 1/2019-12/2021, n=94) had improved mOS relative to the 134 pts in the earlier group (30.6 vs 17.4 mos, p=0.02) despite similar number of average Tx lines (2.4 vs 2.5). **Conclusions:** During a decade when significant changes occurred in the aUC Tx landscape, pts treated at an academic center had lower Tx attrition rates than those described in real world settings during a similar timeframe. Notably, pts who started Tx after 1/2019 had improved OS relative to pts who started Tx earlier, despite similar number of average Tx lines. This finding may be driven by higher ORR to 1st and 2nd Tx lines in pts treated more recently. Validation in other academic centers and larger cohorts is needed. Research Sponsor: None.

Characteristic	All Pts (N=237)	Earlier Group (N=134)	Later Group (N=103)	p^1
Median age at Tx Start (Years)	68.5	67.3	69.1	0.33
Sex – N (%)				0.52
Male	164 (69)	95 (71)	69 (67)	
Female	73 (31)	39 (29)	34 (33)	
Primary Tumor Location – N (%)				N/A
Lower Tract	168 (71)	97 (73)	71 (69)	
Upper Tract	57 (24)	35 (26)	22 (21)	
Multiple/Unk	12 (5)	2 (1)	10 (10)	
1st line Tx	237	134	103	N/A
Tx type – N (%)				
Plat-based	81 (34)	48 (36)	33 (32)	
IO	113 (48)	76 (58)	37 (36)	
Other	43 (18)	10 (7)	33 (32)	
1st line ORR	43%	31%	57%	**<0.0001**
2nd line Tx	133 (56)[2]	74 (55)[2]	59 (57)[2]	0.75[3]
Tx type – N (%)				
Plat-based	30 (23)	23 (31)	7 (12)	
IO-based	56 (42)	30 (41)	26 (44)	
Other	47 (35)	21 (28)	26 (44)	
2nd line ORR	35%	28%	44%	0.08
3rd line Tx	61 (26)[2]	35 (26)[2]	26 (25)[2]	0.88[3]
Tx type – N (%)				
Plat-based	15 (25)	12 (34)	3 (12)	
IO	12 (20)	5 (14)	7 (27)	
Other	34 (56)	18 (51)	16 (62)	
3rd line ORR	24%	19%	33%	0.27

[1]Compare earlier vs later pts; [2]% of 1st line; [3]Compare % receiving this Tx line.

A phase II study of tislelizumab (T) monotherapy as neoadjuvant treatment for cisplatin-ineligible high risk upper tract urothelial carcinoma (UTUC).

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Background: Platinum-based chemotherapy is standard of care after radical nephroureterectomy for patients with high risk UTUC. However, more than half of UTUC patients may suffer from severe renal function loss which limits the use of cisplatin. Here we report the efficacy and safety results of T in the neoadjuvant treatment of patients with high risk UTUC who are ineligible for cisplatin-based chemotherapy. **Methods:** Eligible patients had high risk UTUC defined as pathological high-grade UTUC (either by endoscopic biopsy or urinary cytology) and/or invasive aspect on radiological examination(cT2-T4a N0/X M0) and/or hydronephrosis, ECOG PS 0-2, no prior systemic therapy and ineligible for cisplatin. Patients with variant histology on biopsy were included. Patients were given T 200mg IV every 3 weeks for at most 4 cycles followed by surgery (radical nephroureterectomy or ureteral resection or endoscopic ablation). CTU or contrast enhanced MRI examination was performed before the third dose and another before the surgery. The primary endpoint was pCR(pT0N0). The secondary endpoint included PaR(< pT2N0) and safety. **Results:** 16 patients were recruited between Mar 2021 and Sep 2022: median age was 65 years(46-71), 13(81.3%) male, 14(87.5%) cT3-cT4, 4(25%) cN+. All patients received at least 2 doses of T but 7 patients didn't accept all 4 doses as planned. 9 patients received radical nephroureterectomy, 1 patient received endoscopic ablation, 3 patients received segmental ureteral resection. 3 patients declined surgery due to disease progression or adverse events. Best radiological tumor response before surgery were 6(37.5%) cPR, 7(43.8%) cSD and 3(18.7%) cPD. Overall, 4 patients achieved pCR(25%) after surgery, among which 3 patients received radical nephroureterectomy. 1 patient received endoscopic ablation with no residual disease observed in specimens and was assessed as pCR after surgery with no recurrence observed 1 year after surgery. 7 patients were evaluated as < pT2N0. Grade 3/4 TRAE was 18.8%. No new safety signals were observed. **Conclusions:** The trial demonstrated a promising pCR rate of neoadjuvant tislelizumab in patients with high risk UTUC who were ineligible for cisplatin-based chemotherapy. Further exploratory analysis is ongoing to investigate underlying correlation between tumor immune microenvironment and treatment response. Clinical trial information: NCT04672330. Research Sponsor: None.

Effects of perioperative chemotherapy on prognosis in muscle invasive bladder cancer treated with radical cystectomy.

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Background: We aimed to evaluate the effect of the number of neoadjuvant chemotherapy (NAC) cycles and the adding adjuvant chemotherapy (AC) after NAC in muscle-invasive bladder cancer (MIBC) on overall survival (OS). **Methods:** This multicenter retrospective study included 2674 patients with MIBC who underwent radical cystectomy (RC) from 36 institutions within the Japanese Urological Oncology Group. Among them, we selected 1687 patients with cT2-4NxM0 who were treated with RC alone or RC plus perioperative chemotherapy. We compared the effect of the number of NAC cycles (2 vs. ≥3 cycles) and the addition of AC on OS. Cox proportional-hazards regression was used to assess the association of treatment received with OS. **Results:** Of 1687 patients, 946 were treated with NAC with a median of 3 cycles. Use of NAC significantly prolonged OS compared to the RC alone. The pathological complete response rate was not significantly different between the 2 cycles (22.9%) and ≥3 cycles (27.5%, P = 0.112) groups. OS was not significantly different between the groups (P = 0.559). Multivariable Cox regression analysis showed that pathological high-risk (ypT2–4, pT3–4, or pN+) or cisplatin ineligibility were significantly associated with poor OS, but not the number of NAC cycles (P = 0.238). We identified 942 pathologically high-risk patients after RC who were eligible for AC. We observed no significant OS improvement with addition of AC after NAC as intensive peri-operative chemotherapy. The primary limitation is selection bias from confounding by clinical indication. **Conclusions:** The impact of 3 or more NAC cycles and the addition of AC on OS in MIBC patients treated with RC may be limited. Research Sponsor: None.

Blue light cystoscopy versus white light cystoscopy for the detection of bladder cancer in China: An analysis of unpublished clinical trial and real-world data.

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Background: Blue light cystoscopy (BLC) is superior to white light cystoscopy (WLC) in detection of bladder cancer, but no multi-center studies have been conducted in China with modern 4K LED equipment. The objective of this post hoc analysis of a randomized controlled trial (RCT) and a real-world study (RWS) was to compare BLC with WLC in the detection of bladder cancer and to determine the similarity between the RCT and RWS. **Methods:** In RCT (NCT05600322), patients with known or suspected bladder cancer were enrolled at seven hospitals in China from November 2022 to June 2023. In the prospective RWS, patients with known or suspected bladder cancer were enrolled at Hainan General Hospital from December 2022 to July 2023. Patients received intravesical HAL (Hexvix, Photocure ASA) and underwent WLC before BLC (System blue, Richard Wolf GmbH). Some patients were randomized to WLC to avoid observational bias. The primary endpoint was the proportion of patients with histologically confirmed tumors (Ta, T1, or CIS) who have at least one such lesion found by BLC but not by WLC. Secondary endpoints included, detection of CIS, lesion specific detection rate, false positive rates, and adverse events (AE). **Results:** 158 patients were enrolled in RCT, in which 37 patients were training patients, six patients were randomized to not undergo BLC, one patient withdrew. 114 patients remained in the full analysis set. 19 patients were enrolled in RWS. In patients confirmed with Ta, T1, or CIS, 42/97 patients (43.3%) in RCT and 4/12 patients (33.3%) in RWS had at least one confirmed lesion found by BLC but not by WLC (all $p<0.0001$). 11/114 patients (9.6%) with CIS in RCT and 1/14 patients (7.1%) with CIS in RWS showed at least 1 additional confirmed CIS lesion found by BLC but not by WLC. In RCT, detection rates for PUNLMP, CIS, Ta, T1 and T2-T4 tumors were NA, 94.7%, 100%, 98.2% and 100% for BLC and NA, 42.1%, 76.1%, 91.2% and 100% for WLC, respectively. In RWS, detection rates for PUNLMP, CIS, Ta, T1 and T2-T4 tumors were NA, 100%, 100%, 100% and 100% for BLC and NA, 50%, 81%, 100% and 100% for WLC, respectively. The false-positive rate was 23.2% and 16.0% for BLC and WLC in RCT and was 25.0% and 15.4% in RWS, respectively. In RCT, 200 AEs were observed in 95 patients, all mild to moderate, of which 191 were classified as unrelated to HAL. In RWS, 16 AEs were observed in 15 patients, all mild and were all unrelated to HAL. **Conclusions:** Both RCT and RWS confirm the superiority of BLC based on innovative LED technology with HAL over WLC in detection of bladder cancer in Chinese populations, especially CIS, and HAL is well tolerated. Clinical trial information: NCT05600322. Research Sponsor: None.

Immune checkpoints blockade therapies' efficacy and toxicity in patients with impaired renal function in metastatic bladder cancer.

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Background: In this study, we reported the real-life results of data from impaired renal patients with urothelial carcinoma who were treated with immune checkpoint blockade therapies (ICT). **Methods:** This study included metastatic urothelial carcinoma patients treated with at least one course of ICT. Impaired renal function was defined as a glomerular filtration rate [GFR] less than 60 mL/min. The patients were categorized into 3 different groups GFR≥60mL/min (normal), 60–30mL/min (low), and less than 30 mL/min (very low) based on GFR. The primary endpoints were the overall response rate (ORR), overall survival (OS), duration of response with ICT, and safety. Median follow-up and OS were estimated using the Kaplan-Meier method. **Results:** Data from 174 eligible patients were analyzed, 4% of these patients received the ICT as the first line, 83.3 % as the second line, and 12.7 % as the third or more line of treatment. One hundred-five(60.3%) of patients were GFR normal, 26.4% were GFR low with 30–60 mL/min, and %13.2 were very low group. The median follow-up time was 52 (1.15–62) months. ORR for GFR normal, low, and very low groups were 36% (n=38), 26% (n=12), and %31 (7); p=0.2, respectively. The median duration of response for GFR normal, low, and very low groups were 47.2 months (95% CI, 24.5–51.4), 33.1 months (95% CI, 26.9–47), and 23.5 months (95% CI, 12.2–43.7); p=0.01, respectively. The Median OS rate for GFR normal, low and very low groups were 11.9 (7.2–16.5) months, 4.7 (1.8–7.7), and 6.8 (1.1–13.6) months, p=0.015, respectively. In univariate analysis, liver metastases, baseline creatinine clearance less (GFR) than 60 ml/min, ECOG PS (1 ≥), and hemoglobin levels < 10 mg/dl were all significantly associated with OS. Three of the adverse prognostic factors according to the Bellmunt criteria were independent of short survival: liver metastases HR=1.6; 95% CI 1.02-3.52; p= 0.043), ECOG PS (1 ≥) HR=2.3; 95% CI 11.05-2.44; p=0.029), and hemoglobin level < 10 mg/dl HR=1.5; 95% CI 1.07-2.34; p: 0.021). In addition, GFR <60 ml/min HR=1.6; 95% CI 1.12-1.80; p=0.02, maintained a significant association with OS in multivariate analysis. GFR normal, low, and very low groups experienced %62.9, 54.3%, and 43.5% of treatment-related adverse events of any grade, respectively. There are no significant differences among each group(p=0.2). Also, treatment-related death and discontinuation were insignificant among each group. **Conclusions:** Long-term follow-up of real-world data confirms that the overall survival rate and durable response rate with ICT were higher in patients with GFR >60mL/min. On the other hand, we demonstrated that ICT was effective and a long durable response was seen in a group of patients with renal impairment who did not have an effective systemic treatment option, The safety profile was consistent with prior reports and similar in each group. Research Sponsor: None.

BladderGATE: Atezolizumab + intravesical BCG (bacillus Calmette-Guerin) upfront combination in patients with high risk non-muscle invasive bladder cancer (NMIBC)—Phase I-II ONCOSUR study.

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Background: Intravesical Bacillus Calmette-Guerin (BCG) induction + BCG maintenance after transurethral resection is the current standard of care for patients (pts) with high-risk non-muscle invasive bladder cancer (NMIBC). Recurrence rate at 2 years and 5 years are around 30-40% and 70-80% respectively. Atezolizumab is a IgG1 monoclonal antibody targeting PD-L1 and is associated with long-term durable remissions in pts with metastatic urothelial cancer (MS. van der Heijden. Eur Urol 2021) and for pts with unresponsive NMIBC (PC. Black. Eur Urol 2023) with excellent results. Atezolizumab in combination with standard BCG could provide synergistic benefit for pts with NMIBC. BladderGATE (NCT04134000) is a phase Ib-II study which evaluates the safety and efficacy of upfront atezolizumab + intravesical BCG in pts with high-risk NMIBC. **Methods:** Pt had confirmed histopathology of high-risk NMIBC, BCG naïve or stopped >2 years ago, WHO PS 0-2 and adequate hematologic and organ function. Dose-escalation design to identify DLT and MTD (9 pts) and to evaluate safety and efficacy in an expansion cohort (30 pts) were programed. Pt received six weekly induction instillations, and maintenance instillations at 3, 6 and 12 months + intravenously atezolizumab 1200 mg every 3 weeks, up to 1 year. Urine/blood and tissue samples were collected for translational and biomarker correlative study. Primary objective is disease free survival. Secondary objectives include safety profile and quality of life. **Results:** Finally 36 pt were included, median age 70 years, 86% men, 61% of pt were former smokers, 22% smokers and 17% had never smoked, and tumor size was ≥3 cm in 44% of pt. With a 22 months median follow-up, 56% of pt had completed BCG treatment and 89% had received adequate BCG treatment (5 induction plus at least 2 maintenance instillations). Thirteen pts discontinued atezolizumab due to immune-related AEs (7 pts) (g2 dermatitis, g3 hepatitis, encephalitis, pneumonitis, myocarditis, adrenal insufficiency and psoriasis), due to early-relapse disease (3 pts) and progressive-disease (3 pts). All irAEs were solved and no toxic death were reported. Of the 36 pts analyzed, 6 pts showed local recurrence (17%), 5 pts with high-risk NMIBC (14%) and 1 pt with low-risk NMIBC, 1 pt with UTUC, and 3 pts with local muscle invasive bladder cancer progressive-disease (8 %). Preliminary 2-year disease free survival is 72.8% (95% CI: 56.1% - 89.5%). **Conclusions:** The combination strategy of atezolizumab + intravesical BCG upfront in high-risk NMIBC pts appears feasible and safe. A 14% of 2-years local recurrence-rate and 8% of local progressive-disease are promising results, pending to randomized Ph3 ALBAN study data (GETUG). Supported by Roche-Spain. Clinical trial information: NCT03425201. Research Sponsor: Roche.

Bladder-sparing treatment for muscle-invasive bladder carcinoma: A single-center, single-arm clinical study of sequential neoadjuvant chemotherapy followed by tislelizumab neoadjuvant immunotherapy.

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Background: Althoughradical cystectomy (RC) in combination with cisplatin-based neoadjuvant chemotherapy is the gold-standard for muscle-invasive bladder carcinoma (MIBC), bladder-sparing treatment have emerged to be an alternative choice for patients who are concerning about the life quality after surgery. The optimal strategy for bladder-sparing treatment such as trimodal therapy (TMT) showed similar effect with RC. Since the TRUCE-01 has illuminated considerable response of neoadjuvant immunotherapy in MIBC, we aim to study whether neoadjuvant chemotherapy plus immunotherapy can improve the bladder-sparing rate in MIBC patients. **Methods:** 30 planned patients with MIBC (T2-4a N0-1 M0) received cisplatin 70 mg/m^2 or carboplatin AUC 4.5 on days 1 every 3 weeks (Q3W) plus gemcitabine 1000 mg/m^2 on the 1st and 8th day of each 21-day cycle x 4 cycles. Tislelizumab 200 mg was administered on the 14th day of each 21-day cycle at the 3rd and 4th cycles. CT and cystoscopy imaging were carried out to evaluate disease progression. After the 4th treatment, radical cystectomy, partial cystectomy or TURBT were perform in accordance with the disease status. For continuous bladder-spare treatment, 2 additional cycles of tislelizumab were performed. Bladder-sparing rate was settled as exploratory endpoints based on 2-years follow-up and predictive biomarker will be analyzed. **Results:** To date, 21 of 30 pts have been enrolled and 17 pts have completed the regimen. 2 pts were excluded because of complicating with other disease (suffering cerebral infraction or rectal cancer during the trail), and 2 pts voluntarily quitted due to intolerance of chemotherapeutic adverse effect (fatigue and gastrointestinal symptoms). 2 pts partially response to the therapy and received RC after disease progression. 1 pt have no response to the therapy and received palliative care as unsuitable for surgery. The resting 10 of 17 pts successfully preserved their bladder by achieving pT0 (58.8%) after treatment. Among them 3 pts have been followed up over 1 year and no relapse was observed. **Conclusions:** These data support neoadjuvant chemotherapy plus immunotherapy a feasible bladder-sparing choice for patients with MIBC. Further completed follow-up data and biomarker analysis will accurately identify patients who are suitable for this therapy. Clinical trial information: ChiCTR2100050763. Research Sponsor: None.

Atezolizumab plus personalized neoantigen vaccination (PGV001) in patients with urothelial cancer.

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Background: Most patients (pts) with urothelial cancer (UC) treated with immune checkpoint inhibitors (ICIs) do not respond. Given that features associated with restrained antitumor immunity and high neoantigen burden have correlated with response to ICI, stimulating antitumor immunity with neoantigen vaccination is an attractive approach to overcome ICI resistance. This study assessed atezolizumab in combination with PGV001, a personalized genomic neoantigen vaccine, in the adjuvant and metastatic settings. **Methods:** This single-arm pilot study (NCT03359239) enrolled pts with UC for treatment in the adjuvant (≥pT3/pN+ who declined or were ineligible for adjuvant chemotherapy; or ≥ypT2/ypN+ after neoadjuvant chemotherapy) or metastatic (disease progression after chemotherapy, or "switch maintenance" for stable disease after chemotherapy) setting. Neoantigen prediction was performed using the OpenVax computational pipeline. After an initial priming vaccination course (cycle 1), pts received atezolizumab 1200 mg intravenously every 3 weeks for up to 12 months (adjuvant) or 24 months (metastatic) and PGV001 with poly-ICLC on subsequent days every 3 weeks during cycles 2-5 and 9. The primary endpoints were feasibility and safety, including the number of neoantigens identified and peptides synthesized per pt, vaccine production time, proportion of consented pts with prepared vaccine, and proportion of treatment-eligible pts completing the priming course. Secondary endpoints included immune monitoring of vaccine-induced neoantigen specific T cells. **Results:** Between 12/2018 and 8/2020 12 pts were enrolled. The median neoantigens identified per pt was 103 (range 60-388). Vaccines containing 9-10 synthetic long peptides (24-25mer) were prepared for 92% (11/12) of consented pts over a median of 153 days (95% CI 151-181 days). 100% (10/10: 4 adjuvant, 6 metastatic) of pts eligible for the treatment phase completed the priming course. All evaluated pts demonstrated the emergence of *ex vivo* T cell responses as reflected by IFNγ production, including circulating multi-functional $CD4^+$ and $CD8^+$ neoantigen-specific T cell responses upon expansion. At a median follow up of 32 months, 4/4 patients treated in the adjuvant setting were free of recurrence and 2/5 pts with metastatic UC achieved an objective response. The single pt treated in the switch maintenance setting had no evidence of disease, off all treatment, at 33 months. The most common treatment-related adverse events were grade 1 injection site reactions, fatigue, and fever. One pt developed grade 3 immune-related hepatitis. **Conclusions:** Atezolizumab plus PGV001 was feasible, safe, and induced neoantigen-specific T cell immunity in all evaluated pts. To our knowledge, this is the first report of combination neoantigen vaccination plus ICI in the adjuvant setting in UC. Neoantigen vaccination plus ICI warrants further evaluation. Clinical trial information: NCT03359239. Research Sponsor: Genentech.

Role of thromboprophylaxis during neoadjuvant chemotherapy before radical cystectomy in patients with bladder cancer: Results of a multicenter retrospective cohort study.

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Background: Patients undergoing radical cystectomy are at risk of developing venous thromboembolic events (VTE), with most VTEs occurring during neoadjuvant chemotherapy. The ASCO Clinical Practice Guideline Update recommends thromboprophylaxis in cancer patients with a high risk of VTE and a low risk of bleeding. However, the risks of VTE and bleeding with or without thromboprophylaxis in bladder cancer patients scheduled for radical cystectomy have not been well evaluated. **Methods:** We conducted a retrospective cohort study of patients with non-metastatic bladder cancer undergoing cystectomy across 28 centers in 13 countries between 1990 and 2021. Inverse probability weighting analyses were performed to estimate the effect of thromboprophylaxis during neoadjuvant chemotherapy on VTE and bleeding. **Results:** Of 4886 patients, 4631 (95%) received neither thromboprophylaxis nor anticoagulation during chemotherapy. Thromboprophylaxis during neoadjuvant chemotherapy was prescribed in 151 (3%) patients mainly being enoxaparin (80%) with a median duration of 94 (range 38 to 104) days. In inverse probability weighting analyses, patients with thromboprophylaxis compared to patients without thromboprophylaxis during chemotherapy had not only a lower VTE (HR 0.32 [95% CI, 0.12 to 0.81], p-value = 0.016) but also a lower bleeding risk (HR 0.03 [95% CI, 0.09 to 0.12], p-value: <0.0001). **Conclusions:** In this retrospective analysis, the benefit of thromboprophylaxis during neoadjuvant chemotherapy before cystectomy is in line with data from randomized trials in other malignancies. Our data suggests thromboprophylaxis seems protective against VTEs during neoadjuvant chemotherapy in bladder cancer patients planned for cystectomy. The ASCO guidelines recommending thromboprophylaxis during chemotherapy should therefore also be regarded as a standard of care in patients treated with neoadjuvant chemotherapy before cystectomy. Research Sponsor: None.

Association of HER2 expression in advanced urothelial carcinoma (aUC) and treatment outcomes with immune checkpoint inhibitors and enfortumab vedotin.

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Background: HER2 immunohistochemistry (IHC) is not routinely assessed in patients (pts) with aUC, but it is an emerging predictive biomarker with the advent of HER2-targeting agents. aUC outcomes with respect to HER2 status following treatment with immune checkpoint inhibitors (ICIs) and enfortumab vedotin (EV) are unknown. **Methods:** We retrospectively identified pts with aUC and available biopsies tested for HER2 IHC and fluorescence in situ hybridization (FISH). HER2 status was assessed using modified GI criteria as HER2 high (IHC 3+ or IHC 2+/FISH+), HER2 low (IHC 2+/FISH- or IHC 1+) or HER2 negative (IHC 0). Pt characteristics and outcomes were abstracted from chart review. We compared outcomes following ICI monotherapy and EV-based regimens in pts with HER2-high or HER2-low tumors relative to HER2-negative, and HER2-positive (≥IHC 1+) tumors relative to HER2-negative. Observed response rate (ORR) evaluated by local investigator was compared in pts with scans after ≥1 treatment cycles using logistic regression, while progression-free survival (PFS) and overall survival (OS) from treatment start were assessed using the Kaplan-Meier method and Cox proportional hazards model. **Results:** Biopsies from 181 pts with aUC obtained from 3/2016 – 3/2023 were tested for HER2 (34 high, 88 low, 58 negative, 1 indeterminate). In this group, 43 pts received ICI [38 (88%) pembrolizumab; 5 (12%) atezolizumab] and 37 EV [31 (82%) monotherapy; 6 (18%) combination regimen]. Pt characteristics and outcomes are shown in the Table. Among pts treated with EV, HER2-negative pts had decreased PFS (HR: 0.18, 95% CI 0.03 – 0.94, p=0.04) relative to HER2-high. No other differences were noted for any cross-group comparison. For pts treated with ICI, no differences in outcomes were observed for any comparisons based on HER2 status. **Conclusions:** In this single institution retrospective analysis, pts with aUC and HER2-high IHC expression had longer PFS relative to pts with HER2-negative expression when treated with EV-based regimens. No differences were observed in ICI outcomes based on HER2 expression. These hypothesis-generating results should be validated in larger cohorts. Research Sponsor: None.

	ICI (N=43)	EV (N=37)
Median Age at Tx Start (yrs)	73	72
Gender – n (%)		
Male	25 (58)	25 (68)
Female	18 (42)	12 (32)
Primary Tumor Site – n (%)		
Bladder	31 (72)	27 (73)
Upper Tract	6 (14)	7 (19)
Unknown/Other	6 (14)	3 (8)
Histology – n (%)		
Pure Urothelial	21 (49)	19 (51)
Variant Component	19 (44)	16 (43)
Pure Variant	3 (7)	2 (6)
Prior lines of Therapy – n (%)		
<2	35 (81)	20 (54)
≥2	8 (19)	17 (46)
***Outcomes by HER2 Status,* mos (95% CI)**		
HER2 High, N	7	8
ORR	20% (1/5)	63% (5/8)
mPFS	2.4 (2.0 – NR)	15.4 (6.4 – NR)
mOS	12.6 (6.8 – NR)	18.2 (10.1 – NR)
HER2 Low, N	24	20
ORR	35% (7/20)	37% (7/19)
mPFS	5.6 (3.4 – NR)	5.0 (4.0 – NR)
mOS	30.6 (15.0 – NR)	24.0 (8.5 – NR)
HER2 Negative, N	12	9
ORR	40% (4/10)	38% (3/8)
mPFS	4.0 (1.5 – NR)	4.5 (1.9 – NR)
mOS	5.5 (2.1 – NR)	NR (3.83 – NR)

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

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Background: Avelumab 1L maintenance is recommended as standard of care by international treatment guidelines for pts with aUC that has not progressed with 1L platinum-based chemotherapy, based on level 1 evidence from the phase 3 JAVELIN Bladder 100 trial (NCT02603432). In the trial, avelumab 1L maintenance + best supportive care (BSC) significantly prolonged overall survival (OS) and progression-free survival (PFS) vs BSC alone (median OS, 23.8 vs 15.0 mo; HR, 0.76 [95% CI, 0.63-0.91]; 2-sided p=0.0036). The long-term safety of avelumab 1L maintenance was also demonstrated. It is estimated that 25% of the world's population will have BMI ≥30 by 2035, and high BMI is a risk factor for bladder cancer. We report post hoc analyses of long-term outcomes from JAVELIN Bladder 100 in pts with high BMI (≥30) at baseline. **Methods:** Eligible pts with unresectable locally advanced or metastatic UC without progression after 4-6 cycles of 1L platinum-based chemotherapy were randomized 1:1 to receive avelumab 10 mg/kg every 2 wk + BSC (n=350) or BSC alone (n=350). The primary endpoint was OS; secondary endpoints included PFS and safety. **Results:** At data cutoff (June 4, 2021), median follow-up was ≥38 mo in both arms. In the avelumab + BSC and BSC alone arms, 67 and 55 pts had high BMI at baseline, respectively. In these pts, median OS was 20.8 mo (95% CI, 16.9-34.4) with avelumab + BSC vs 12.7 mo (95% CI, 8.1-26.6) with BSC alone (HR, 0.77 [95% CI, 0.49-1.21]); 2-y OS rates were 47.8% vs 37.6%, respectively. Median PFS by investigator was 5.6 mo (95% CI, 3.7-7.5) with avelumab + BSC vs 2.1 mo (95% CI, 1.9-4.0) with BSC alone (HR, 0.64 [95% CI, 0.42-0.97]); 2-y PFS rates were 23.5% vs 11.3%, respectively. Long-term safety in pts with high BMI was generally consistent with the overall safety population (Table). **Conclusions:** This exploratory analysis shows the long-term efficacy and tolerability of avelumab 1L maintenance in pts with high BMI in JAVELIN Bladder 100, with no new safety concerns identified. These results further support the use of avelumab 1L maintenance as standard of care in pts with aUC who are progression free after 1L platinum-based chemotherapy, including pts with high BMI. Clinical trial information: NCT02603432. Research Sponsor: This trial was sponsored by Pfizer and was previously conducted under an alliance between the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945) and Pfizer; This analysis was sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany.

	Treated Pts with High BMI		Overall Safety Population	
Patients, n (%)	Avelumab + BSC (n=67)	BSC (n=54)	Avelumab + BSC (n=344)	BSC (n=345)
Any-grade TEAE	66 (98.5)	44 (81.5)	338 (98.3)	270 (78.3)
Grade ≥3 TEAE	43 (64.2)	17 (31.5)	185 (53.8)	89 (25.8)
Any-grade TRAE	54 (80.6)	2 (3.7)	269 (78.2)	6 (1.7)
Grade ≥3 TRAE	18 (26.9)	0	67 (19.5)	0
TEAE leading to death	3 (4.5)	7 (13.0)	7 (2.0)	24 (7.0)
TRAE leading to death	1 (1.5)*	0	2 (0.6)	0
Any-grade immune-related adverse event	24 (35.8)	0	111 (32.3)	6 (1.7)
Any-grade infusion-related reaction	15 (22.4)	0	75 (21.8)	0

TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event. *Attributed to immune-mediated nephritis by the investigator.

Clinical efficacy of lurbinectedin in metastatic neuroendocrine carcinomas of the genitourinary tract: Multi-institutional real-world experience.

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Background: Neuroendocrine carcinomas (NEC) of the genitourinary (GU) tract, including small cell (SC) NEC and large cell (LC) NEC, are rare aggressive malignancies. Although highly sensitive to cisplatin-based chemotherapy, GU metastatic NEC (mNEC) have limited data to support next therapies. Lurbinectedin, a marine-derived alkylating drug and a selective inhibitor of oncogenic transcription and DNA repair pathways, is FDA-approved for small cell lung cancer (SCLC) after progression on frontline platinum-based therapy, with a disease control rate (DCR) of 68.6%. It is unknown whether DCR is similar in SCLC and GU mNEC. **Methods:** We report the first multi-institutional series (n=14) of lurbinectedin in GU mNEC. Imaging-based best overall responses (BOR) were noted as complete (CR), partial (PR), stable (SD), progressive (PD) or non-evaluable (NE). DCR includes CR, PR, and SD. We use the Kaplan-Meier method for overall survival (OS) and progression-free survival (PFS) from lurbinectedin start date. We define duration of response (DoR) from response date to progression or last contact date for patients (pts) with CR or PR. **Results:** Most pts had a median age at metastasis of 70.5 years (ICR: 64-74.5) [Table]. Primary locations were bladder (7/14, 50%), prostate (5/14, 35.7%) and ureter (2/14, 12.3%). Histology at diagnosis mostly consisted of mixed or pure SCNEC, with one exception of LCNEC. Most pts had visceral disease, prior immunotherapy and at least 2 prior lines of therapy for mNEC before lurbinectedin (8/14, 57.1%). DCR was 6/14 (42.8%), including 5 bladder pts and 1 prostate pt. Among bladder pts, BOR included one CR (1/7, 14.3%) for the LCNEC case, 2 PR (2/7, 28.6%), 2 SD (2/7, 28.6%) and 2 PD (2/7, 28.6%). Most prostate and ureteral pts either progressed on lurbinectedin or were NE (Prostate: 1 PR, 2 PD, and 2 NE; Ureteral: 1 PD and 1 NE). For all 14 pts, median OS was 11.47 months (95% CI: 2.17-13.63) and median PFS was 2.8 mo (1.4-10.9). Median DoR was 7.38 mo (2.3-9.53) for 4 responding pts (CR or PR). Treatment was stopped due to progression (9/14, 64.3%), three adverse events [thrombocytopenia, electrolyte abnormalities, cerebrovascular accident] (3/14, 21.4%), and pt preference (1/14, 7.1%). **Conclusions:** Lurbinectedin offers encouraging responses (DCR: 5/7, 71.4%) close to those in SCLC, in previously treated bladder mNEC. One CR was noted for a bladder pt with LCNEC. Responses were less appreciated in prostate and ureteral mNEC due to NE responses and limited number. Larger cohorts are needed to confirm survival benefit and genetic analyses are warranted to identify characteristics of responders. Research Sponsor: None.

Characteristics n=14		n (%)
Prior platinum in metastatic disease (met.)		**11 (78.6%)**
Prior IO in met.		**10 (71.5%)**
Visceral met. at lurbi start	**Any**	**13 (92.8%)**
	Liver	**9 (64.3%)**
	Bone	**8 (57.1%)**
	Brain	**1 (7.1%)**
Prior lines of treatment in met.	**0**	**1 (7.1%)**
	1-2	**10 (71.5%)**
	3-4	**3 (21.4%)**

Efficacy outcomes and biomarker analysis from phase II trial of escalating doses of neoadjuvant atezolizumab in patients with muscle-invasive urothelial carcinoma ineligible for cisplatin-based chemotherapy.

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Background: There are no current standard of care options for patients (pts) with muscle-invasive bladder cancer (MIBC) ineligible for cisplatin-based chemotherapy (cisplatin). This trial investigated the safety and efficacy of escalating doses of neoadjuvant atezolizumab (ATZ) prior to radical cystectomy (RC) (NCT02451423). **Methods:** This single-arm, single institution, phase II trial investigated treatment with 1 (n=6), 2 (n=6) or 3 (n=11) cycles of ATZ (1200 mg IV every 3 weeks) in pts with MIBC. Key inclusion criteria were urothelial carcinoma of the bladder (T2-T4a,N0-1,M0), cisplatin-ineligibility, and eligibility for RC. High-risk pts (>pT2 or LN+ at RC) could receive adjuvant ATZ for up to 16 total cycles. Primary efficacy endpoint was pathologic complete response (pCR; pT0/Ta/TisN0). Secondary endpoints included rate of pathologic downstaging (≤T1N0), 2-year recurrence-free survival (RFS), overall survival (OS), and biomarker assessments of pre and post-treatment biopsies. Pts had RC between 7/2016 and 6/2021. The censor date for survival outcomes was 9/10/2023, representing the final efficacy analysis. **Results:** A total of 23 pts received ATZ; 1 pt was excluded from efficacy analyses due to lack of confirmed MIBC (≥T2). Among 22 included pts, median age was 70, 74% were men, 83% Caucasian; reasons for cisplatin-ineligibility were renal impairment (37%), hearing loss (27%) or neuropathy (9%); remainder declined cisplatin (27%). At enrollment, cT2/T3/T4 rates were 77%, 14%, and 9%, while 9% were cLN+. All pts completed intended treatment and had RC in the defined timeframe (>3 weeks from last and <12 weeks from first treatment). pCR at RC was 14% (3/22), occurring in pts receiving 1 and 2 cycles of ATZ. Pathologic downstaging (≤pT1N0) was achieved in 23% (5/22), occurring at all three dose levels. Adjuvant ATZ was given to 8 pts. Another 4 pts received off-study adjuvant therapy with cisplatin (3) or nivolumab (1). After median follow-up of 51.4 months from RC, mRFS and mOS were Not Reached. Two-year RFS and OS were 77% and 90%. In 13 pts with available paired pre and post treatment samples, there was significant increase in T-cell % following ATZ (Wilcoxon signed rank test, $p<0.05$), driven by increase in % and density of CD8+ T-cells ($p<0.05$). All T-cell populations were significantly more abundant in tumor than in adjacent normal tissue post-treatment but not pre-treatment ($CD3^+$,$CD3^+CD8^+$, $CD3^+CD4^+$, $p<0.001$ for all; $CD4^+FOXP3^+$, $p=0.01$). **Conclusions:** Neoadjuvant ATZ results in durable long-term survival rates in cisplatin-ineligible pts with MIBC. These data are comparable to previously reported trials with immunotherapy based regimens, despite a lower pCR rate. Changes suggestive of T-cell migration into the tumor microenvironment were observed following ATZ treatment. Clinical trial information: NCT02451423. Research Sponsor: Genentech.

Datopotamab deruxtecan in locally advanced/metastatic urothelial cancer: Preliminary results from the phase 1 TROPION-PanTumor01 study.

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Background: Datopotamab deruxtecan (Dato-DXd) is an antibody-drug conjugate consisting of a humanized anti-TROP2 IgG1 monoclonal antibody covalently linked to a highly potent topoisomerase I inhibitor payload via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker. Dato-DXd has shown encouraging antitumor activity and a manageable safety profile in patients (pts) with solid tumors. We report preliminary results in pts with advanced/metastatic (a/m) urothelial cancer from the ongoing phase 1 TROPION-PanTumor01 study (NCT03401385). **Methods:** Pts with unresectable a/m urothelial cancer treated with ≥1 prior line of therapy received intravenous Dato-DXd 6 mg/kg Q3W. Primary study objectives were safety and tolerability. Secondary endpoints were objective response rate (ORR; complete response [CR] + partial response [PR]), and disease control rate (DCR; CR + PR + stable disease) per RECIST 1.1 by BICR. This is the first data disclosure from this cohort in an ongoing expansion cohort study. **Results:** At data cutoff (May 18, 2023), 18 pts had received Dato-DXd. Median follow-up was 9.1 (range 5–17) months; 6 (33.3%) pts were receiving ongoing treatment. Median age was 63.5 (range 46–79) yrs. Pts were heavily pretreated, 15 (83.3%) had received ≥3 prior regimens. All pts received prior immunotherapy, 17 (94.4%) prior platinum-based chemotherapy, and 4 (22.2%) prior taxanes. Treatment-emergent adverse events (TEAEs) occurred in 100% (any grade [gr]) and 44.4% (gr ≥3) of pts, and drug-related TEAEs occurred in 94.4% (any gr) and 16.7% (gr ≥3) of pts. No drug-related serious AEs were reported, and no TEAEs associated with death were observed. Any gr TEAEs associated with reduction, interruption, and discontinuation of treatment were reported in 11.1%, 33.3%, and 5.6% of pts, respectively (Table). Adjudicated drug-related interstitial lung disease (gr 2) occurred in 1 (5.6%) pt. Confirmed ORR was 27.8% (95% CI 9.7–53.5); 1 pt achieved a CR and 4 achieved a PR. DCR was 77.8% (95% CI 52.4–93.6). Clinical evaluation of this cohort is ongoing and updated results will be presented. **Conclusions:** In heavily pretreated pts with a/m urothelial cancer, Dato-DXd demonstrated a tolerable and manageable safety profile with encouraging antitumor activity. Dato-DXd is being evaluated in pts with urothelial cancer as part of the phase 1/2 TROPION-PanTumor02 (NCT05460273) and the phase 2 TROPION-PanTumor03 (NCT05489211) studies. Clinical trial information: NCT03401385. Research Sponsor: Daiichi Sankyo.

Safety summary.

Patients, n (%)	N=18
TEAE	18 (100)
Grade ≥3	8 (44.4)
Associated with dose reduction	2 (11.1)
Associated with dose interruption	6 (33.3)
Associated with treatment discontinuation	1 (5.6)
Drug-related TEAE	17 (94.4)
Grade ≥3	3 (16.7)*
SAE	4 (22.2)
Drug-related SAE	0

*Stomatitis (n=2), lymphocyte count decreased (n=1). SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Infusion-related reactions with immune checkpoint inhibitors in genitourinary cancers: A systematic review and meta-analysis.

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Background: Immune checkpoint inhibitors (ICIs) are widely used to treat genitourinary cancers, particularly urothelial carcinoma (UC) and renal cell carcinoma (RCC). Infusion-related reactions (IRRs) have been reported in up to 20% of all patients treated with ICIs. However, the risk of IRRs varies with the type of ICI and the accurate incidence in genitourinary cancers remains unclear. We undertook a systematic review and meta-analysis to determine the incidence of IRRs in patients with genitourinary cancers treated with ICIs. **Methods:** We performed a systematic search of PubMed/MEDLINE, Embase, and Web of Science to identify phase 3 randomized clinical trials (RCTs) evaluating ICIs (cytotoxic T-lymphocyte-associated protein 4 [CTLA-4], programmed cell death protein 1 [PD-1], and programmed death-ligand 1 [PD-L1] inhibitors) in patients with UC and RCC. The odds ratio [OR] of grade 1-5 and grade 3-5 IRRs was calculated and pooled by the random-effect model meta-analysis. Meta-analysis was performed based on study types as follows: 1) Studies with a design "ICI plus treatment A (including placebo/observation) vs. treatment A", 2) Studies evaluating ICI monotherapy vs. chemotherapy in patients with UC, and 3) Studies assessing ICI plus vascular endothelial growth factor tyrosine kinase inhibitors (VEGF-TKIs) vs. sunitinib in patients with RCC. When IRRs were reported in studies evaluating oral VEGF-TKIs, IRRs were referred to as hypersensitivity or anaphylactic reactions, defined in each RCT. **Results:** We identified 12 RCTs with 10,001 participants for the meta-analysis, out of which one evaluated a CTLA-4 inhibitor while the others evaluated PD-1 or PD-L1 inhibitors. The addition of ICIs to other systemic therapies was associated with significantly higher rates of grade 1-5 IRRs (OR=2.90, 95% confidence interval [CI]: 1.16-7.29, p = 0.02) but not of grade 3-5 IRRs (OR=2.98, 95% CI: 0.64-13.74, p = 0.16). When compared to chemotherapy, PD-1 or PD-L1 inhibitor monotherapy was not associated with an increase in either grade 1-5 (OR=0.86, 95% CI: 0.25-2.95, p = 0.81) or grade 3-5 IRRs (OR=1.13, 95% CI: 0.07-18.19, p = 0.93) in patients with UC. When compared to sunitinib in patients with RCC, the combination of ICI plus VEGF-TKIs was not associated with an increase in either grade 1-5 (OR=5.43, 95% CI: 0.62-46.07, p = 0.13) or grade 3-5 IRRs (OR=3.49, 95% CI: 0.64-19.04, p = 0.15). Sensitivity analysis performed by removing studies evaluating avelumab did not alter the overall results (data will be presented). **Conclusions:** Compared to the previous standard of care without ICIs, therapies with ICIs were not associated with increased IRRs in genitourinary cancers. However, the addition of ICIs to other systemic therapies was associated with an increased incidence of IRRs. The latter merits further prospective evaluation and careful consideration while designing clinical trials. Research Sponsor: None.

Real-world (rw) treatment patterns, sequencing, and outcomes in patients (pts) with locally advanced or metastatic urothelial carcinoma (la/mUC) receiving avelumab first-line maintenance (1LM) in the US.

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Background: Avelumab 1LM is recommended in international guidelines for pts with la/mUC and disease control after 1L platinum-based chemotherapy (PBC). This study describes the treatment landscape after FDA approval of avelumab in June 2020 by examining pt characteristics, treatment patterns and sequencing, and rw outcomes in pts treated with avelumab 1LM. **Methods:** This noninterventional retrospective study identified pts with la/mUC who received avelumab 1LM in the US using data from Flatiron Health's electronic health record database. Pts aged ≥18 y with ≥2 visits on/after Jan 1, 2011, diagnosed with la/mUC from Jan 1, 2019 - Dec 31, 2022, treated with 1L PBC followed by avelumab 1LM on/after Jul 1, 2020, ≤90 d after 1L PBC discontinuation, and with no disease progression ≤14 wk after 1L PBC were included. Treatment patterns in 1LM, second line (2L), and third line (3L) were assessed. Clinical outcomes, including rw progression-free survival (rwPFS), rw overall survival (rwOS), time to treatment discontinuation (TTD), and time to next treatment (TTNT) from 1LM or 2L initiation, were assessed using Kaplan-Meier methods. **Results:** 214 avelumab 1LM-treated pts met eligibility criteria. Median age was 70 y; most pts were male (77%), White (66%), and had an ECOG of 0-1 (77%). Median follow-up from 1LM was 8.7 mo. Of 96 (45%) pts who received 2L treatment post avelumab 1LM, enfortumab vedotin (EV) monotherapy (55%) was most common, followed by carboplatin-based therapy (11%). Of 40 (42%) pts who received 3L treatment, EV monotherapy was most common (25%), followed by sacituzumab govitecan (20%). Median PFS and OS from start of avelumab 1LM was 5.1 (95% CI 4.1-7.0) and 23.8 (95% CI 18.2-NE) mo. Median TTNT from avelumab 1LM initiation was 7.0 (95% CI 5.6-8.6) mo. Of pts who received 2L EV, median rwPFS and rwOS from 2L initiation were 4.9 (95% CI 3.9-8.8) and 11.2 (95% CI 6.8-NE) mo. Further rw outcomes are presented in the Table. **Conclusions:** Clinical outcomes in this study are aligned with those of the JAVELIN Bladder 100 trial (NCT02603432), further supporting avelumab 1LM as a standard of care. With each additional line of therapy, substantial treatment attrition and less favorable clinical outcomes were observed. This study provides insights into the sequencing of treatments and management of pts with la/mUC after disease progression with avelumab 1LM in this rapidly evolving therapeutic landscape. The use of more effective upfront therapies may decrease the attrition rates. Research Sponsor: This study was sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

Avelumab 1LM-treated pts (N=214)	Outcome	Median (95% CI), mo
From 1LM (N=214)	rwPFS	5.1 (4.1-7.0)
	rwOS	23.8 (18.2-NE)
	TTNT	7.0 (5.6-8.6)
	TTD	4.9 (4.2-6.5)
From 2L EV (N=53)	rwPFS	4.9 (3.9-8.8)
	rwOS	11.2 (6.8-NE)
	TTNT	5.8 (5.2-9.5)
	TTD	4.7 (4.2-8.5)

NE, not estimable.

Trends over time in the proportion of sequential treatment and overall survival in patients with metastatic urothelial carcinoma in real-world practice.

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Background: New approaches involving immune checkpoint inhibitors (ICIs) and antibody-drug conjugates prolong overall survival (OS) in patients with metastatic urothelial carcinoma (mUC). However, the access to such systemic therapy in clinical practice is suboptimal, and whether these agents improve OS in patients with mUC over time remains unclear. In the present study, we investigated the OS trend from the initiation of first-line therapy with these agents to identify changes due to the medication and time of treatment initiation. **Methods:** We retrospectively evaluated 195 patients who received platinum-based chemotherapy as a first line treatment. The patients were treated with chemotherapy, pembrolizumab, avelumab, or enfortumab vedotin (EV) sequentially and were divided into the following three groups: chemotherapy period (April 2009–June 2017; P1), pembrolizumab period (July 2017–December 2020; P2), and avelumab and EV period (January 2021–August 2022; P3) based on the regulatory approval. Data cutoff was set at July 31, 2023. **Results:** OS was prolonged over time by the new therapeutic agents, and median OS was 11, 25, not reached, and 35.5 months for patients who were treated with chemotherapy, pembrolizumab, avelumab, or EV, respectively. However, median OS was 14, 18 months, and not reached in P1, P2 and P3, respectively. Analysis by periods showed that OS was significantly longer in P2 than in P1 (HR = 0.62, 95% CI: 0.43–0.89, P = 0.009) and in P3 than in P1 (HR = 0.47, 95% CI: 0.28–0.78, P = 0.015). No difference was observed in OS between P2 and P3 (HR = 0.66, 95% CI: 0.36–1.20, P = 0.21). Overall, the proportion of patients who received ICIs increased over time, as indicated by the fact that 77 and 95 patients received ICIs (pembrolizumab or avelumab) in P2 and P3, respectively. However, the prevalence of the treatment with EV was only 24%, and 43% of patients who received pembrolizumab received best supportive care. **Conclusions:** This study showed an improvement in OS over time in patients with mUC in real-world practice and may indicate the importance of not missing the appropriate opportunity to receive sequential treatments. Research Sponsor: None.

Comparative outcomes of radical nephroureterectomy and kidney-sparing surgery in the treatment of high-grade upper tract urothelial carcinoma.

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Background: Patients with upper tract urothelial carcinoma (UTUC) can be managed with either radical nephroureterectomy (RNU) or kidney sparing surgery (KSS) depending on the pathology and patient specific characteristics. Due to the rarity of this disease, high-level evidence is lacking with regard to clinical and oncologic outcomes after surgery. This study aims to compare outcomes of RNU with KSS for patients with high-grade (HG) UTUC. **Methods:** We retrospectively reviewed patients with >1 year follow-up who were treated for HG UTUC at our institution from 2015-2021. Oncologic and clinical outcomes were recorded. Procedure-related burdens, including total number of procedures under anesthesia, anesthesia time, and days hospitalized were collected. **Results:** 65 patients were analyzed, with 46 patients treated via RNU and 19 treated via KSS. There were no differences in the ASA or CCI between patients in the two groups. The 5-year overall survival (OS) was 65.2% (95% CI, 52.8%-80.5%) for RNU and 44.4% (95% CI, 26.5%-74.5%) for KSS. The 3-year metastasis-free survival was 78.3% for RNU and 78.9% for KSS. The 3-year recurrence-free survival, including recurrences in the bladder, was 47.8% (95% CI, 35.4%-64.7%) for RNU and 43.8% (95% CI, 25.1%-76.3%) for KSS. A decline of GFR <10 2 years after surgery occurred in 97.1% of patients treated with RNU and 100.0% of those treated with KSS. The total number of procedures under anesthesia was higher for KSS than RNU at 3.4 +/- 1.7 vs 2.1 +/- 1.7, respectively (p = 0.0155). The total number of TURBTs for KSS and RNU was similar at 0.6 +/- 0.7 vs 1.1 +/- 1.7, respectively (p = 0.9538). The total number of days hospitalized for KSS was similar to RNU at 5.5 +/- 4.3 vs 6.8 +/- 4.6, respectively (p = 0.3579). The total anesthesia time for KSS was 400 +/- 218 min and was 474 +/- 185 min for RNU (p = 0.2561). **Conclusions:** There were similar oncologic and clinical outcomes in patients with HG UTUC treated with either KSS or RNU. Patients treated with KSS saw a higher procedural load. There was a trend towards lower OS for patients treated with KSS but this was not statistically significant, likely due to the small sample size. Larger datasets are needed to further evaluate outcome and treatment burdens of RNU vs KSS as treatment options for patients with HG UTUC. Research Sponsor: None.

	RN	KSS	p-value
N	46	19	
Follow-up, years	2.82 +/- 1.89	2.16 +/- 0.90	0.2485
5-yr overall survival	65.2% [95% CI, 52.8%-80.5%]	44.4% [95% CI, 26.5%-74.5%]	0.22
3-yr metastasis-free survival	78.3% [95% CI, 67.2%-91.1%]	78.9% [95% CI, 62.6%-99.6%]	0.70
3-yr recurrence-free survival	47.8% [95% CI, 35.4%-64.7%]	43.8% [95% CI, 25.1%-76.3%]	0.94
Total # of Operations	2.1 +/- 1.7	3.4 +/- 1.7	0.0155
Total Anesthesia Time (min)	474 +/- 185	400 +/- 218	0.2561
Total Days Hospitalized	6.8 +/- 4.6	5.5 +/- 4.3	0.3579
GFR decline <10 at 2 years	97.1% [95% CI, 91.5%-100.0%]	100% [95% CI, 100.0%-100.0%]	0.081

A retrospective cohort study to monitor real-world safety in patients with locally advanced or metastatic urothelial carcinoma (LA/mUC) treated with sacituzumab govitecan (SG) in the United States.

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Background: Patients with LA/mUC experience poor outcomes, with few treatment options historically available. In April 2021, SG (a TROP-2-directed antibody drug conjugate) received accelerated approval for patients with LA/mUC who progressed after platinum-based chemotherapy and immune checkpoint inhibitor therapy, based on the pivotal TROPHY U-01 trial (NCT03547973). We sought to evaluate SG safety in patients with LA/mUC treated in routine clinical practice in this study. **Methods:** A retrospective cohort of patients aged ≥ 18 years with LA/mUC treated with SG in the United States was evaluated using data from the nationwide Flatiron Health electronic health record–derived de-identified database (from Jan 2011 to Oct 2022). Outcomes included patient characteristics, treatment patterns, adverse events (AEs) of interest incidence, and granulocyte-colony stimulating factor (G-CSF) use. Descriptive statistics were used for data analysis. **Results:** This study included 86SG-treated patients (male, 70%; median age, 71 [range: 25-85] years; 27% with ECOG ≥ 2; 84% treated in community settings). Most patients (71%) received enfortumab vedotin (EV) in the direct prior line. The majority of patients received SG as monotherapy (94%), with most patients overall (99%) receiving SG as second-line (2L) or later. The most common AEs of interest (any grade, overall) were diarrhea (35%), neutropenia (40%) and nausea/vomiting (21%) (Table). Of the 86 patients, 14 (16%) patients were hospitalized, 8 (9%) discontinued SG treatment likely due to AEs/toxicity, and 3 (3%) died during or within 7 days after the line of treatment. During SG treatment, 52% of patients used G-CSF (primary prophylaxis 24%; secondary prophylaxis 19%; therapeutic use 28%). Only 1 (4.5%) patient who had primary G-CSF prophylaxis developed grade ≥ 3 neutropenia. **Conclusions:** This study is the largest analysis of SG use in a real-world population with LA/mUC to date; it provides insights into the safety of SG in this setting. Compared with prior data, this real-world population was older, with poorer functionality, and the majority received EV in the direct prior line. Observed AEs were consistent with the known safety profile of SG and indicate that this sequencing is feasible. Research Sponsor: Gilead Sciences, Inc.

Summary of AEs, n (%)	All (N = 86)	1/2L (n = 11)	3L (n = 31)	4L (n = 25)	5L+ (n = 19)
Diarrhea	30 (35%)	3 (27%)	14 (45%)	5 (20%)	8 (42%)
Neutropenia	34 (40%)	4 (36%)	9 (29%)	10 (40%)	11 (58%)
Grade 2	13 (15%)	3 (27%)	3 (10%)	5 (20%)	2 (11%)
Grade 3	9 (10%)	0 (0%)	5 (16%)	1 (4%)	3 (16%)
Grade 4	7 (8%)	1 (9%)	0 (0%)	2 (8%)	4 (21%)
Nausea or vomiting	18 (21%)	1 (9%)	9 (29%)	4 (16%)	4 (21%)
Urinary tract infection	9 (10%)	1 (9%)	2 (6%)	2 (8%)	4 (21%)
Sepsis	8 (9%)	0 (0%)	4 (13%)	1 (4%)	3 (16%)
Febrile neutropenia	5 (6%)	0 (0%)	2 (6%)	1 (4%)	2 (11%)

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

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Background: Despite advances, effective treatments are needed for patients (pts) with metastatic urothelial carcinoma (mUC). Enfortumab vedotin (EV) is an antibody-drug conjugate (ADC) specific for Nectin-4 that is approved as monotherapy and in combination with pembrolizumab in patients who are cisplatin-ineligible. Cabozantinib (cabo) is a multi-tyrosine kinase that inhibits VEGF, MET and AXL with activity in heavily pretreated mUC. Preclinical data suggests antiangiogenic agents may increase ADC penetration of tumor cells, potentially leading to therapeutic synergy. We report safety and preliminary efficacy data from the dose escalation cohort of an ongoing phase I/Ib trial investigating cabo in combination with EV in mUC. **Methods:** This is a phase I/Ib, open label, single arm, trial at the Winship Cancer Institute of Emory University (NCT04878029). Pts with histologically confirmed mUC who received or were ineligible for platinum chemotherapy and a checkpoint inhibitor are eligible. The phase I dose escalation is a traditional 3+3 design exploring cabo 20 or 40 mg daily with standard dose EV (1.25 mg/kg on days 1, 8, and 15 of a 28-day cycle). The dose expansion cohort is currently enrolling. The primary endpoint of the phase I cohort was safety and tolerability to determine the RP2D. Key secondary objective is preliminary evidence of efficacy via objective response rate (ORR) per RECIST v1.1. **Results:** As of the 22 September 2023 data cut, 6 pts with mUC have been treated. Three pts were enrolled at the cabo 20 mg and 40 mg dose levels, respectively. All are male with median age of 69 (61-85). 4 of 6 patients (66.7%) are white. One serious adverse event (SAE) occurred in the 20 mg cohort (dehydration) and 3 SAEs occurred at the 40 mg dose (neutropenia, acute kidney injury, superior vena cava syndrome); the neutropenia was the singular grade 4 AE. While this represented the sole dose-limiting toxicity of dose escalation, cabo 20 mg daily was selected as the RP2D based on clinical judgment regarding longer-term tolerability. Only one pt in the 40 mg cohort remains on the initial dose. The most common treatment-related AEs are ALT elevation, hypophosphatemia, rash (66%), fatigue, mucositis, AST elevation, hypomagnesemia, eye irritation, hand-foot syndrome, and anorexia (50%). Five pts had a grade 3 AE (83%); the most common were fatigue (33%) and AKI (33%). The ORR was 83% with each of the 5 of 6 responders experiencing a partial response. The median target lesion reduction was 49.7% (31.8-100). **Conclusions:** These preliminary data suggest that the combination of EV and cabo 20 mg daily is safe and tolerable with adverse events previously seen with each agent. Encouraging early evidence of activity has been observed based on response rates. Enrollment of mUC pts into dose expansion with cabo 20 mg daily continues and further results including long-term outcomes and correlatives are forthcoming. Clinical trial information: NCT04878029. Research Sponsor: Exelixis.

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

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Background: MIBC is a systemic disease with a high risk of recurrence after radical cystectomy (RC), that represents the standard of care (SOC) for cisplatin-ineligible pts. Initial data suggest that ABX is active in combination with pembrolizumab in advanced urothelial carcinoma (UC; PMID:32979512). We report results from a phase 2 trial of NIVO + ABX followed by RC and adjuvant NIVO in pts with MIBC (NCT04876313). **Methods:** Eligible pts who were cisplatin unfit or declined cisplatin-based treatment had previously untreated MIBC (clinical stage T2-T4a, N0-1, M0, assessed via CT and MRI scan), Eastern Cooperative Oncology Group performance status ≤ 1, and predominant (> 50%) UC histology. Pts received 4 cycles of NIVO 360 mg Q3W + ABX 125 mg/m2 on Day 1 and 8, Q3W, followed by RC and by 13 administrations of adjuvant NIVO 360 mg Q3W. The primary endpoint was the pathologic complete response rate (ypT0N0; H0: ≤20% and H1≥ 38% in a 2-stage design: ≥9 ypT0N0 were required in stage 1+2). Secondary endpoints were major pathological response (ypT≤1N0), safety (CTCAE v5.0) and event-free survival (EFS). Tumor biomarkers included comprehensive genomic profiling (CGP) and PD-L1 expression, and circulating tumor DNA monitoring (Signatera). **Results:** 31 pts were enrolled from 12/2021 to 06/2023; 17 (54.8%) had a cT3-4 stage, 14 (45.2%) a cT2, 2 (6.4%) had N1 stage, 15 (48.4%) had a variant histology component. All 31 pts concluded the neoadjuvant treatment, 29 having pathological response at data cutoff. A total of 4 pts (14.8%) received <4 cycles of neoadjuvant treatment due to treatment-related adverse events (TRAEs). Four patients had G3 TRAEs, including neutropenia (2), asthenia (1), increased AST/ALT (2), neurotoxicity (1) and acute renal failure (1). The median time from start treatment to RC was 4 months (IQR: 3-4). In total, 11 pts (38%; 95%CI 20.3-55.6) achieved an ypT0N0 response and 21 (72%; 95%CI 55.3-88.3) an ypT≤1N0 response. No disease progressions (PD) occurred during neoadjuvant treatment. After a median follow-up of 10.6 months (IQR: 8-16), one pt had a PD: 12-month EFS was 96.4% (95%CI: 89.9-100). Mean tumor mutational burden (TMB) was 12.3 mut/Mb for ypT0N0 responders vs 5.8 mut/Mb for non-responders. All pts with MRI complete response had a ctDNA-negative assay post neoadjuvant NIVO-ABX. **Conclusions:** The first results from Nure-Combo trial suggest that this novel chemo-immunotherapy combination with NIVO+ABX could be an effective and safe perioperative strategy in pts with MIBC with sustained efficacy post-RC. These results could expand the opportunities of chemotherapy combinations in cisplatin-ineligible pts. Results also strengthen the role of clinical complete response to envision organ-sparing approaches. Clinical trial information: NCT04876313. Research Sponsor: None.

Analysis of neoadjuvant immunotherapy and chemotherapy for muscle-invasive bladder cancer in a national registry.

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Background: Neoadjuvant immunotherapy (NIO) is an exciting new treatment option for muscle-invasive bladder cancer (MIBC). Early-phase trials are encouraging however increased evidence is needed to support its use over Neoadjuvant chemotherapy (NAC). In this study, we sought to assess factors associated with NIO use in MIBC and survival outcomes. **Methods:** The National Cancer Database was used to identify 8,267 patients between 2006 and 2019. Patients were included based on urothelial bladder cancer diagnosis, clinical staging (T2-4N0-3M0), and receipt of NIO or NAC prior to radical cystectomy. NAC and NIO patient groups with similar clinical and demographic characteristics were defined using a 1:1 propensity score matching method. Categorical and continuous were assessed with chi-square test and independent sample T-test, respectively. Survival outcomes were compared using Kaplan-Meier analyses. **Results:** Mean age at diagnosis was significantly higher in NIO patients (70.5 years, SD 8.93) compared to NAC patients (65.64 years, SD 8.99) ($p<.001$). NIO patients were associated with higher Charlson-Dayo scores ($p=.028$), high income ($p=.027$), treatment at an academic facility ($p<.001$), and at a facility greater than 30 miles away ($p=.002$) when compared to NAC patients. In the matched analysis, these characteristics were all similar. NAC use was associated with increased rates of T down-staging to pT0-1 compared to NIO (47/118, 39.8% vs 20/109, 18.3%; $p<0.001$). Conversely, NIO use was associated with increased rates of T up-staging to pT3-4 compared to NAC (38/109, 34.9% vs 23/118, 19.5%; $p=0.009$). Kaplan-Meier analysis demonstrated no difference in overall survival when comparing patients who received NIO and NAC ($p=.477$). **Conclusions:** In this study use of NIO was associated with older and more comorbid patients compared to NAC. We found NIO less effective at achieving pathologic down-staging than NAC. Furthermore, increased rates of pathologic up-staging were observed with NIO use compared to NAC. These findings suggest the clinical benefit of neoadjuvant immunotherapy remains unclear. Research Sponsor: None.

Variables	NAC (n=172)	NIO (n=172)	p-value[a]
Pathologic Up-staging to T3-T4	23, 19.5%	38, 34.9%	0.009
Yes	95, 80.6%	71, 65.1%	
No			
Pathological Down-Staging to T0-T1	47, 39.8%	20, 18.3%	<0.001
Yes	71, 60.2%	89, 81.7%	
No			
Pathologic N Up-staging	5, 16.1%	2, 19.4%	0.521
Yes	107, 83.9%	101, 80.6%	
No			
Pathologic N Down-Staging	5, 4.5%	2, 1.9%	0.298
Yes	107, 95.5%	101, 98.1%	
No			
Pathologic M staging	4, 6.5%	0, 0.0%	0.051
0	58, 93.5%	57, 100.0%	
1			

[a]Significance calculated with Chi-square test. NAC: neoadjuvant chemotherapy; NIO: neoadjuvant immunotherapy.

NEXT: A phase 2 study of nivolumab adjuvant to chemoradiation in patients (pts) with localized urothelial carcinoma.

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Background: Definitive chemoradiation (CRT) is the preferred bladder preservation treatment for non-metastatic urothelial cancer (nmUC). The NEXT trial (NCT03171025) evaluated the efficacy of adjuvant nivolumab to definitive CRT in pts with nmUC. **Methods:** This multicenter study enrolled nmUC pts who received standard-of-care CRT. Nivolumab 480 mg was administered every 4 weeks for up to 12 doses. Primary endpoint: failure-free survival (FFS) at 2 years (yrs). Secondary endpoint: safety. This is the first efficacy and safety analysis after completion of enrollment, and correlation of disease risk features, and changes in plasma cell-free DNA (cfDNA) with outcomes. Shallow whole genome sequenced data from plasma cfDNA was mapped to the human reference genome (HG19), and copy number instability (CNI) Score (Oncocyte) was derived from statistically significant altered regions. **Results:** From 8/03/2017 to 1/25/2023, 28 pts were enrolled. The median age was 72 yrs (range 54-86 yrs). Ten patients (36%) had ≥ T3 and/or N+ disease. At time of data cut-off (9/14/23), median nivolumab cycles were 8.5 (range 1-12), and median follow-up was 11 months (range 6 - 45). FFS at 2 yrs (n=24) was 38.7 % (95% CI 23%-65.2%). Disease relapse occurred in 16 pts, of which 9 had local recurrences. Grade ≥3 treatment-related adverse events (AEs) occurred at a frequency of 10.7%. These were elevated transaminases, diarrhea, and polymyalgia rheumatica. Grade 3 radiation therapy oncology group (RTOG) AEs occurred in 2 pts. One or more high-risk disease features (ie. plasmacytoid differentiation, T4, N+, multiple tumors, tumors > 5 cm, residual disease before CRT, CIS, and hydronephrosis) were present in 22 pts (79%). In a Cox proportional hazards model, the number of high-risk features was a significant predictor of progression (p = 0.006). Each additional high-risk feature was associated with a hazard ratio for progression of 1.77 (95% CI 1.17-2.67). Median CNI (mCNI) on C1D1 of nivolumab in relapsed pts was 31 (range 3-232) vs. 24 (range 3-109) in pts with ongoing response. The mCNI on C4D1 for pts who progressed was 15.5 (range 6-371) vs. 9 (range 3-65) in pts with ongoing response. Oncogenic gene copy number changes and the associated pathways associated with progression are listed in the table. **Conclusions:** Adjuvant nivolumab to CRT for nmUC has promising efficacy with tolerable AEs, even in pts with high-risk disease. Disease relapse correlates with high-risk clinical features and CNI in plasma cfDNA. Oncogenic copy number changes in genes involved in DNA repair, RTK-RAS-PI3K, WNT, and cell cycle pathways are present in cfDNA of those who progressed (Table). Clinical trial information: NCT03171025. Research Sponsor: Bristol Myers Squibb Pharmaceutica.

Gene changes and associated pathways correlated with progression.

Copy Number Changes	Pathways
MAP2K4 del; ALK amp	RTK/RAS Pathway
BRCA1 del	DNA Repair
ARID1A del; TSC2 del	PI3K Pathway
WT1 del; SOX2 amp	WNT Pathway
NKX2.1 amp	Cell Cycle
MYC amp	Myc Pathway

Sequential endoluminal gemcitabine and docetaxel versus bacillus Calmette–Guérin for the treatment of high-grade upper tract urothelial carcinoma.

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Background: BCG is currently the only endoluminal treatment option for high-grade (HG) upper tract urothelial carcinoma (UTUC). Gemcitabine/Docetaxel (Gem/Doce) has shown promising efficacy as a treatment for HG UTUC, though a comparison to BCG is lacking. We report the outcomes of patients treated with endoluminal Gem/Doce versus BCG for non-invasive HG UTUC. **Methods:** A retrospective review of patients treated with Gem/Doce versus BCG for clinically non-invasive HG UTUC was performed. Treatment was instilled via nephrostomy or retrograde ureteral catheter. Induction instillations were performed weekly for 6 weeks. If disease free, maintenance therapy for Gem/Doce was monthly for 6 months and a single 3 week mini-cycle for BCG. Recurrence was defined as biopsy-proven disease or HG cytology. Progression was defined as development of muscle invasion, metastases, or death due to cancer. **Results:** The final cohort included 59 patients with 71 treated upper tract units; 36 received BCG and 35 received Gem/Doce. Median follow-up was 62 months in the BCG group and 29 months in the Gem/Doce group. Indication for treatment included a positive HG cytology in 78% and 89% of the BCG and Gem/Doce groups, respectively; the remaining patients in each group presented with pathologically-confirmed HG disease. The 2-year estimates for recurrence-free and nephroureterectomy-free survival were 57% and 87% for the BCG group and 56% and 100% for the Gem/Doce group, respectively (Table). Upon multivariable analysis, treatment with Gem/Doce was not associated with an increased risk of recurrence versus BCG (HR 0.78, 95%CI 0.33-1.85; p=0.57). In total, 19% of patients receiving BCG and 15% of patients receiving Gem/Doce experienced a grade 3+ adverse event. The development of any symptoms was not statistically different between treatment groups (p=0.28). There were two deaths recorded during the study period, one in each treatment group. **Conclusions:** Endoluminal Gem/Doce and BCG have similar oncological outcomes and major AE rates in the treatment of HG UTUC. Further prospective evaluation is warranted. Research Sponsor: John & Carol Walter Family Foundation.

Summary of survival outcomes.

		6 Months	12 Months	24 Months	Median Follow-Up Among Survivors (Months)
Recurrence-Free Survival	BCG	82% (64-91%)	76% (57-87%)	57% (39-72%)	55
	Gem/Doce	94% (78-98%)	78% (60-89%)	56% (36-72%)	27
Progression-Free Survival	BCG	97% (80-100%)	94% (77-98%)	84% (65-93%)	51
	Gem/Doce	93% (74-98%)	93% (74-98%)	93% (74-98%)	25
Nephroureterectomy-Free Survival	BCG	97% (80-100%)	97% (80-100%)	87% (70-95%)	40
	Gem/Doce	100%	100%	100%	24
Cancer-Specific Survival	BCG	97% (80-100%)	97% (80-100%)	94% (77-98%)	98
	Gem/Doce	96% (76-99%)	92% (73-98%)	92% (73-98%)	29
Overall Survival	BCG	97% (80-100%)	97% (80-100%)	94% (77-98%)	89
	Gem/Doce	96% (76-99%)	92% (73-98%)	89% (69-96%)	30

Note: RFS and NFS are evaluated per UT unit. PFS, CSS, and OS are evaluated per patient.

Extended follow-up report of a randomized phase II trial comparing gemcitabine and cisplatin with or without berzosertib in patients with advanced urothelial carcinoma.

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Background: Gemcitabine with cisplatin (GC) remains a frontline treatment option for patients (pts) with metastatic urothelial cancer (mUC). Preclinical synergy has been noted when combining cisplatin with berzosertib, a selective ATR inhibitor. This trial sought to determine the effect of addition of berzosertib to GC on clinical outcomes in mUC; here we present final study results with extended follow-up. **Methods:** This open-label, randomized study enrolled pts with confirmed mUC, no prior cytotoxic therapy for metastatic disease, > 12 months since perioperative chemotherapy and eligible for cisplatin based on standard criteria. Pts were randomized to receive either GC plus berzosertib (Arm A) or GC alone (Arm B). In Arm A, cisplatin 60 mg/m^2 IV was given on D1, gemcitabine 875 mg/m^2 IV on D1 & 8, and berzosertib 90 mg/m^2 IV on D2 & 9 of a 21-day cycle. In Arm B, cisplatin 70 mg/m^2 IV was given on Day 1 (D1) and gemcitabine 1000 mg/m^2 IV on D1 & 8 of a 21-day cycle. The primary endpoint of the study was progression-free survival (PFS), with secondary endpoints including response rate (RR), overall survival (OS) and toxicity. **Results:** A total of 87 pts (median age 67; M:F 68:19) were randomized, 46 pts to Arm A and 41 pts to Arm B. With a median follow-up of 37.7 months (95% CI: 28.3, 39.3), median PFS in Arm A was 6.2 month and 7.1 months in Arm B (HR: 1.3 [95% CI: 0.8-2.2], p=0.1). RR was 54% in Arm A and 63% in Arm B. Median OS was 10.9 months in Arm A and 19.8 months in Arm B (HR: 1.2 [95% CI: 0.7-2.1], p=0.2). Common > Grade 3 adverse events included anemia (Arm A: 57%, Arm B: 24%), neutropenia (Arm A: 36.9%, Arm B: 26.8%), thrombocytopenia (Arm A: 58.7%, Arm B: 39%). **Conclusions:** With >18 months of extended follow-up, there remained no PFS or OS benefit with the addition of berzosertib to GC, compared to GC alone in a biomarker unselected population. Myelosuppression was common despite reduced dosing of cisplatin and gemcitabine suggesting that combining ATR inhibition with platinum-based chemotherapy may not be feasible in pts with mUC. Clinical trial information: NCT02567409. Research Sponsor: National Cancer Institute.

Preliminary efficacy and safety results from ReBirth: A phase II study of risk-based bladder-sparing therapy for MIBC.

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Background: Trimodal therapy (TMT) has achieved long-term survival and persistent oncologic control in selected MIBC patients, however, tailored treatment using biomarkers based on chemotherapy plus PD-1 inhibitor responses is currently absent. Furthermore, the safety and efficacy of hypo-fractionated radiation in combination with PD-1 inhibitors and concurrent chemotherapy is worth exploring. **Methods:** This is a two-stage, single-arm, phase II trial recruiting cT2-4aN0-1M0 MIBC pts. Based on results of cystoscopy, urine cytology, imaging and MRD detection after first stage (Tislelizumab (T) 200 mg on D1, Cisplatin (C) 70 mg/m^2 on D1 and Gemcitabine (G) 1000 mg/m^2 on D1 and D8 Q3W for 3-4 cycles), pts achieving cCR (cT0, cTa) are treated with T, while the other pts receive T and chemoradiotherapy (whole bladder 44Gy/16 fractionation combined with C as radiosensitizer). 1-year BIDFS rate is the primary endpoint. Secondary endpoints include 2-year MFS rate, 2-year BIDFS rate and safety. Tissue and urine samples will be obtained for genetic profiling and biomarker research. **Results:** The preliminary efficacy and safety are reported this time. As of September 20, 2023 (median follow up: 258 (49-415) days, 25 pts with a median age of 64 (36-77) years were enrolled and 96% are male. 19 pts with cT2 (57.14%), cT3 (33.33%) and cT4 (9.52%) tumors were evaluable. 2 pts were assessed as N1. 14/19 pts (73.68%) achieved cCR and maintained a sustained response. Based on positive urine cytology and MRD, 5 pts were classified as non-cCR (2 pts in cT3N0M0, 2 pts in cT4N0M0 and 1 pt in cT2N0M0). Due to RC (2 pts achieving ypT0N0 and 1 pt achieving ypT2N0) and incomplete treatment cycles, 6 pts were excluded from the efficacy analysis set. BFS rate at 1 yr is evaluated in 6 pts (2 pts received hypo-fractionated on the second stage) and the rate is 100%. TRAEs were found in 19 of 25 pts (76%). The grade 3-4 TRAEs observed (8%) was adrenal cortical insufficiency and immuno-therapy related colonitis. Hematological AEs (32%), renal insufficiency (24%), pruritus (20%), and fatigue (20%) are the most common AEs. During hypo-fractionated radiation, no new safety signs were discovered. **Conclusions:** The preliminary findings indicate a potential efficacy and manageable toxicity during the two-stage treatment. Enrollment is still ongoing, and long-term efficacy will be proved. Clinical trial information: NCT05531123. Research Sponsor: None.

Sequencing of erdafitinib (erda) and enfortumab vedotin (EV) in patients (pts) with fibroblast growth factor receptor (FGFR2/3) altered (alt) advanced urothelial cancer (aUC): Analysis of UNITE database.

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Background: The optimal therapy sequencing in aUC with FGFR2/3 alt is unclear. FGFR inhibition may increase Nectin-4 expression. We hypothesized that outcomes with EV would be more favorable when given after E compared to before E in pts with aUC harboring FGFR2/3 genomic alt. **Methods:** Pts with FGFR2/3 alts who received EV only (EVo), E then EV (E->EV), or EV then E (EV->E) were included. Overall survival (OS) measured from E or EV start (based on agent given first) and progression-free survival (PFS) measured from EV start were assessed with KM method and group comparison by log rank test with Cox proportional hazards regression model. Variables with $p \leq 0.2$ were included in multivariate analysis (MVA). Wilcoxon rank sum and Fisher's exact test were used to compare continuous and categorical variables, respectively. Observed response rate (ORR) was compared between groups using $\chi 2$ test. **Results:** Among 633 pts from 16 US sites, 487 had NGS data, and 94 (19%) had FGFR2/3 alterations with 24 receiving E->EV, 15 EV->E, and 55 EVo. Median age: 72 yrs; 87% Caucasian, 65% primary bladder tumor, 73% pure urothelial histology, 76% BMI <30, 83% ECOG PS 0-1, 60% visceral metastases (mets) with 23% liver mets, 93% prior IO, and 63% prior Plt. Pts treated with E->EV vs EV->E had similar baseline characteristics, but at EV start ECOG PS 0-1 was 93% in EV->E vs 67% in E->EV (p=0.04). ORR to EV for E->EV pts was 32% (CI- 12%-51%) vs 67% (CI 54%-91%) for EV->E pts (p=0.04). ORR for EVo was 49%. Median OS was 21 months (mo) E->EV, 19 mo EV->E, and 12 mo EVo; median PFS was 5, 5, 6 mo, respectively. Univariate analysis (UVA) and MVA results are shown in Table. In MVA, longer OS was seen in pts who received both EV and E vs EVo. **Conclusions:** We showed longersurvival in pts with FGFR2/3 alt aUC who received both EV and E regardless of sequence, which may reflect guarantee-time bias. Additional limitations include retrospective nature, modest sample size, no central scan review, lack of data for pts who received E only, selection and confounding biases. Larger prospective studies are needed to determine optimal sequencing and putative biomarkers. Research Sponsor: None.

	UVA OS: HR (95% CI)	p	MVA OS: HR (95% CI)	p	UVA PFS: HR (95% CI)	p	MVA PFS: HR (95% CI)	p
Visceral Mets (yes vs no)	1.49 (0.83-2.68)	0.18	1.56 (0.86-2.83)	0.14	1.49 (0.92-2.4)	0.10	1.46 (0.87-2.44)	0.15
EV->E vs EVo	0.54 (0.26-1.09)	0.08	0.51 (0.25-1.02)	0.06	1.32 (0.73-2.4)	0.36	1.49 (0.79-2.81)	0.22
E->EV vs EVo	0.53 (0.27-1.01)	0.05	0.52 (0.27-1.01)	0.05	1.61 (0.94-2.76)	0.08	1.64 (0.91-2.96)	0.10
EV + E (regardless of sequence) vs EVo	**0.53 (0.3-0.93)**	**0.03**	**0.52 (0.3-0.9)**	**0.02**	1.47 (0.93-2.33)	0.10	1.57 (0.97-2.55)	0.07
Prior IO (yes vs no)	-	-	-	-	**0.4 (0.18-0.88)**	**0.02**	0.48 (0.19-1.21)	0.12
BMI at EV start (>30 vs <19)	-	-	-	-	0.3 (0.09-1.09)	0.07	**0.23 (0.06-0.86)**	**0.03**

Livmoniplimab with or without budigalimab in patients with advanced solid tumors: Results from the combination therapy in the urothelial carcinoma dose expansion cohort.

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Background: Checkpoint inhibitors (CPIs) are approved for treating advanced urothelial carcinoma (UC). However, many patients (pts) present with/develop resistance and new therapies are urgently needed. The release of active transforming growth factor beta-1 (TGF-β1) from the glycoprotein-A repetitions predominant (GARP):TGF-β1 complex on regulatory CD4+ T cells suppresses antitumor response. Inhibiting active TGF-β1 release from the GARP:TGF-β1 complex could address CPI resistance in UC. Livmoniplimab (livmo), an antibody targeting the GARP:TGF-β1 complex, is being investigated as monotherapy and in combination with budigalimab (budi), an anti–PD-1 antibody, in a phase 1 study (NCT03821935). We present expanded results from the livmo + budi dose expansion (EXP) in pts with UC. **Methods:** This is a global, dose escalation (ESC) and EXP study in pts (≥18 yr) with advanced solid tumors; the UC EXP cohort enrolled pts with UC of the bladder and urinary tract that progressed on platinum-based therapy and a CPI in the metastatic setting. The maximum tolerated dose was not reached in the ESC part, and pts in EXP cohorts received the maximum administered dose of 1500 mg livmo (IV, Q2W) and 500 mg budi (IV, Q4W) until disease progression/intolerable toxicity. The primary efficacy endpoint was ORR per RECIST v1.1. Additional efficacy outcomes included DOR and PFS. Safety and PK were also assessed. **Results:** As of 30 Mar 2023, 200 pts were enrolled, 57 in ESC and 143 in livmo + budi EXP, including 48 pts in the UC EXP cohort. For the UC cohort, median age was 66 yr (49–85), 77% of pts were male, 40%/60% had ECOG PS 0/1, and median prior lines of therapy was 3 (1–9). Livmo PK was not impacted by budi coadministration and no on-treatment anti-drug-*antibodies* were detected. TEAEs were observed in 100% of pts; most common were pruritus (44%) and decreased appetite (21%). Grade 3/4 TEAEs occurred in 23 pts (48%), with anemia and malignant neoplasm progression (10% each) being the most common; 11 pts (23%) died but no death was related to livmo or budi. TRAEs were observed in 29 pts (60%)/26 pts (54%) for livmo/budi; pruritus (livmo: 33%; budi: 31%) and rash (17% for both) were most common. Among the 45 response evaluable pts, best response rate was 24% (n=11; 95% CI: 12.9, 39.5); confirmed ORR was 18%. Median restricted mean DOR was 7.9 mo (95% CI: 6.0, not reached); median/75th percentile PFS were 1.8 mo (95% CI: 1.6, 4.2)/8.0 mo (95% CI: 2.7, 14.9). **Conclusions:** Livmo + budi had manageable safety and promising efficacy in pts with advanced UC that progressed on platinum-based therapy and a CPI. ORR in the UC cohort (pts postprogression with platinum + CPI therapy) are comparable with ORR in CPI-naive pts with pembrolizumab (KEYNOTE-045) and nivolumab (CheckMate 275) monotherapy. A subpopulation of pts in the UC cohort had a durable response to livmo + budi. Clinical trial information: NCT03821935. Research Sponsor: AbbVie.

Punch: Preliminary results from a phase II study of intra-arterial chemotherapy (IAC) combined with tislelizumab and bacillus Calmette-Guerin (BCG) in high-risk non-muscle-invasive bladder cancer (HR NMIBC).

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Background: Previous studies have proved IAC could reduce the recurrence and progression of HR NMIBC. The KEYNOTE-057 study has supported the benefits of PD-1 inhibitor in HR NMIBC patients (pts). Our study was established to evaluate the efficacy and safety of IAC combined with tislelizumab and BCG as a bladder-preserving treatment for HR NMIBC pts. **Methods:** This open-label, single arm phase II study enrolled BCG-naïve HR NMIBC pts with papillary tumors (high-grade Ta or T1 tumors). Firstly, the papillary tumors should be removed all visible lesions by transurethral resection of bladder tumor (TURBT). Secondly, angiographic catheter was placed into the internal iliac arteries with Seldinger's percutaneous technique, cisplatin (60 mg/m^2) and epirubicin (50 mg/m^2) were administered arterially in day 1 (D1), every 3 weeks for 2-4 cycles. And pts received tislelizumab 200 mg IVGTT in D1, every 3 weeks for 2-4 cycles. Finally, pts received 18 instillations of BCG plus at least 8 cycles of tislelizumab (200 mg IVGTT, every 3 weeks). Specifically, pts were started on an induction course of BCG with 6 instillations every week, followed by maintenance with 3 instillations every 2 weeks and 9 instillations every 4 weeks. The primary end point was disease-free survival (DFS) rate at 12 months (defined as no reappearance of high grade or T1 tumors or clinical stage development after the therapy). Secondary end points were bladder-preservation rate, OS and safety. Our study estimated a DFS rate at 12 months was no less than 55% and the study would enroll 27 pts. **Results:** By Sep. 2023, 13 eligible pts were enrolled. Ten pts were analyzed (male 80.0%; median age 58 years (39-77); pure TCC 80.0%; median tumor size 2.5 cm (0.6-5.4); multiple papillary tumours=60.0%; high-grade Ta=40.0%, T1=60.0%). Median follow-up was 16.4 months (10.8-33.9), the mean number of IAC cycles was 2.4, mean number of tislelizumab cycles was 15.8, and the median BCG instillations was 16 (11-18). The DFS rate at 12 month was 90.0% (95%CI, 71.5%-98.6%). One pt showed reappearance of high-grade Ta and received TURBT. The bladder-preservation rate at 12 months was 100% (95%CI, 100%-100%). The OS rate at 12 months was 100% (95%CI, 100%-100%). 3 pts experienced treatment related adverse events, including nausea (n=1, G2), myalgia (n=1, G2), fatigue (n=1, G2), neutropenia (n=1, G2) and fever (n=1, G3). **Conclusions:** Our preliminary results supported the use of IAC combined with tislelizumab and BCG as a promising bladder-preserving strategy for HR NMIBC pts. Clinical trial information: ChiCTR2200067146. Research Sponsor: None.

Tislelizumab in combination with gemcitabine plus cisplatin as neoadjuvant therapy for lymph node-positive bladder cancer: Results of a prospective study.

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Background: Although multiple single-arm clinical trials have shown promising pathologic complete response (pCR) rates with neoadjuvant ICIs combined with gemcitabine plus cisplatin in MIBC, lymph node-positive bladder cancer is generally excluded. In this study, our specific aim was to compare the efficacy and prognosis of neoadjuvant tislelizumab combined with gemcitabine plus cisplatin in patients with lymph node-positive bladder cancer. **Methods:** In this investigator-initiated study, eligible patients had cT2-T4 N+ M0 MIBC, cisplatin-eligible, and to be planned radical cystectomy (RC). Patients received tislelizumab 200 mg in day 8 (D8), cisplatin 70 mg/m2 D2-4, and gemcitabine 1000 mg/m2 D1 and D8 every 21 days for 3 or 4 cycles. RC was performed within 6 weeks after last dose treatment. The primary endpoint was pathologic complete response (pCR, ypT0). Secondary endpoints included pathologic down-staging (<ypT2), EFS, OS and safety. **Results:** A total of 15 pts were enrolled,14 pts (2 cT2, 7 cT3, 5 cT4) have completed neoadjuvant therapy and underwent RC. One patient declined surgery for personal reasons and received further systemic therapy. In 14 pts evaluable for efficacy, the investigator-assessed confirmed clinical complete response was 21.4% (3/14). Final pathologic results showed that 5 pts (50%) achieved pCR (ypT0N0), 4 ypT1, and 5 ypT2/T3, and 9 patients (<ypT2N0,64.2%) had staging downgrades, with no patients experiencing progression. A complete nodal response (pN0) occurred in 11 (78.5%) pts after tislelizumab +chemotherapy. The median follow-up was 8.9 months, with one death due to multiple metastases and the remaining patients showing no signs of recurrence or metastasis. Median EFS and OS was not reached. Most common neoadjuvant therapy-related AEs of any grade were hematologic toxicities (11/14,78.5%), nausea (9/14,64.2%), vomiting (8/14,57.1%). Grade ≥3 neoadjuvant therapy-related AEs were neutropenia (n = 3), thrombocytopenia (n = 2), anemia (n = 2). One patient discontinued tislelizumab due to AEs. **Conclusions:** The combination of tislelizumab and gemcitabine/cisplatin is clinically active with a manageable safety profile as a neoadjuvant therapy for lymph node-positive bladder cancer. Clinical trial information: NCT04570410. Research Sponsor: None.

The pretreatment neutrophil-to-lymphocyte ratio to predict clinical response to maintenance avelumab therapy in patients with metastatic urothelial cancer.

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Background: It has not been elucidated how preceding first-line chemotherapy affects neutrophil-to-lymphocyte ratio (NLR) and maintenance avelumab therapy. We investigated the relationship between NLR levels just before the initiation of treatment with maintenance avelumab therapy and clinical outcomes in metastatic urothelial cancer (mUC) patients. **Methods:** This retrospective study was analyzed for patients with mUC who received maintenance avelumab therapy between February 2021 and July 2023 at Nagoya University and several affiliated hospitals in Japan. We investigated the relationship between NLR levels just before avelumab therapy and clinical outcomes. All patients were divided into two groups according to NLR levels just before avelumab therapy. A NLR level of ≥3.00 was defined as elevated according to a calculation by a receiver-operation curve analysis. Progression-free survival (PFS) and overall survival (OS) rates were estimated using Kaplan–Meier curves and Cox proportional hazards models. **Results:** The median age and follow-up duration were 73 years (range 49-83 years) and 11.6 months (range 2.4-26.5 months), respectively. The high NLR group consisted of 29 patients (45.3%). Patients in the high NLR group had significantly shorter PFS and OS than those in the low NLR group (p=0.018 and p=0.027, respectively). Similarly, PFS and OS was significantly shortened in patients with NLR levels that had increased during first-line chemotherapy than their counterparts (p=0.018 and p=0.008, respectively). Furthermore, patients in the high NLR group had a significantly lower disease control rate than those in the low NLR group (58.6% vs 91.4%, p=0.003). While there was not a significant association between OS and NLR at the start of first-line chemotherapy (p = 0.763). Multivariate analyses revealed that stable disease as best response to first-line chemotherapy was significantly associated with PFS [hazard ratio (HR), 4.55; p=0.001] and OS (HR, 21.58; p=0.001). **Conclusions:** High NLR levels just before avelumab therapy might be a prognostic factor for mUC patients undergoing maintenance avelumab therapy. Research Sponsor: None.

Pemetrexed (PEM) maintenance versus observation (OBS) in patients (pts) with advanced urothelial carcinoma (aUC) who completed first-line (1L) platinum-based chemotherapy (CTx) without disease progression (PREMIER, KCSG GU16-05).

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Background: Four-to-six cycles ofplatinum-based CTx have been a standard treatment for aUC. However, disease progresses within several months after completion of 1L CTx. Switch maintenance after 1L with effective and safe regimen is an attractive approach to delay disease progression. PEM showed modest response as a salvage CTx in aUC with mild toxicities, which are good candidate for maintenance therapy. We evaluated PEM as switch maintenance therapy versus OBS in pts with aUC whose disease had not progressed. **Methods:** Eligible pts with aUC without disease progression after 4-6 cycles of either cisplatin or carboplatin-based regimen were randomized 1:1 to receive maintenance PEM (500 mg/m^2 IV q3 weeks, up to 16 cycles) or OBS until disease progression, stratified by Galsky et al.'s post-treatment prognostic nomogram for pts with mUC completing 1L cisplatin-based CTx. The primary endpoint was progression-free survival (PFS), and secondary endpoints included overall survival (OS), response rate, and safety. **Results:** This trial was closed early due to poor accrual after avelumab maintenance approval. From Oct 2016 to Dec 2022, a total of 97 pts was randomly assigned to maintenance PEM (n=49) or OBS (n=48). Median age (range) was 69 years (43-90) and 66 (33-82), and male was 63% and 73%, respectively. 1L regimen included gemcitabine plus cisplatin (84% and 83%, respectively), gemcitabine plus carboplatin (12% and 6%, respectively), and MVAC (4% and 10%, respectively). Response to 1L were CR (8% vs. 19%), PR (69% vs. 67%), and SD (22% vs. 15%). Most common metastatic site was abdominopelvic lymph nodes (61% and 65%) and lung (37% and 29%). For PEM group, median administered cycle was 6 (range 1-16), and most common reason for discontinuation was disease progression (53%), followed by completion of planned cycles (20%). With a median follow-up of 19.1 months, median PFS was 6.0 months (mo) [95% confidence interval (CI) 3.4-8.5] for PEM vs. 2.3 mo (1.8-2.7) with a log rank p=0.027, with a hazard ratio (HR) of 0.61 (95% CI 0.40-0.95). Median OS was 25.5 mo (95% CI 11.9-30.1) vs. 26.8 (11.9-41.7) (p=0.607, HR 1.18, 95% CI 0.62-2.26). Anemia (29%), fatigue (18%), and neutropenia (12%) were the most frequent adverse events, and these adverse events were mostly grade 1 or 2, and manageable. **Conclusions:** PREMIER trial showed that switch maintenance PEM prolonged PFS with statistical significance in aUC after 1L platinum-based CTx and had very favorable safety profile. Combination maintenance therapy including PEM needs further investigation. Clinical trial information: NCT03193788. Research Sponsor: None.

Phase 1 dose escalation of SYS6002 (CRB-701), a next-generation nectin-4 targeting antibody drug conjugate (ADC).

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Background: Linker-conjugation of an ADC is a key feature in optimizing highly active and well tolerated agents. For maximal intra-tumoral delivery, linkers need to be highly stable in the systemic circulation yet allow for efficient drug release at the target site. SYS6002 (CRB-701) is a next generation Nectin-4 ADC that makes use of third-generation conjugation technology designed to overcome dose-limiting toxicities observed with the commonly approved linker-payload system involved in agents like enfortumab vedotin (EV). Non-clinically, SYS6002 demonstrates preferential internalization-mediated payload release and a longer half-life than EV. It is being explored in dose escalation on a Q3W schedule, with a view to reducing free-MMAE related toxicities and increasing clinical convenience. **Methods:** The dose escalation/Ph I trial SYS6002-011 spanned 6 dose groups (0.2, 0.6, 1.2, 1.8, 2.7 & 3.6 mg/kg) utilizing Bayesian Optimal Interval (BOIN) design with accelerated titration. The trial is evaluating the safety and tolerability of SYS6002 (CRB-701) to determine the Maximum Tolerated Dose (MTD) and/or the Phase II dose in patients with advanced solid tumors who have failed or were intolerant to standard treatment. Patients were enrolled based on Nectin-4 staining. Beyond determining safety and tolerability, the pharmacokinetic (PK) and preliminarily anti tumor activity of SYS6002 (CRB-701) were assessed. **Results:** Patients enrolled to-date range from 37-76 years, with 69% of patients being female. Disease indications included metastatic urothelial cancer (mUC), cervical cancer, triple-negative breast cancer (TNBC) and colorectal cancer (CRC), having failed a median of 4 prior therapies. All six dose cohorts have been enrolled, with 0.2-2.7 mg/kg cohorts progressing without DLTs and a maximum patient follow up of 10mo. SYS6002 (CRB-701) was well tolerated with most adverse events of Grade 1/2 in severity. Treatment related adverse events of grade 1/2 occurring >20% included corneal epithelial lesions, hematauria, hypertriglyceridemia, hyponatremia, proteinurea, anaemia and dry eye. Of note, the frequency of skin rash and peripheral neuropathy were both 0%. Across the dose escalation cohorts SYS6002 (CRB-701) demonstrated approximately dose-proportional PK and limited accumulation, a longer ADC half-life and a lower free-MMAE conc relative to EV at similar dose levels. Anti tumor responses across multiple doses were observed, with the first confirmed stable disease at 0.6mg/kg and the first confirmed partial response, whose sum of diameters of target lesions decreased by 60% at 1.2 mg/kg. **Conclusions:** SYS6002 (CRB-701) was well tolerated in escalation, and relative to EV demonstrates early signs of a differentiated safety and PK (longer half-life and lower free-MMAE) profile. Continued development of SYS6002 (CRB-701) as both a monotherapy and in combination are planned. Clinical trial information: SYS6002-001. Research Sponsor: None.

Performance of the OncoUrine test on predicting patients who can avoid Re-TURBT and prognosis: A prospective, multicenter clinical study.

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Background: According to European Association of Urology (EAU) guidelines, repeated transurethral resection of bladder tumor (re-TURBT) is recommended in a large percentage of non–muscle-invasive bladder cancers (NMIBC) due to possibility of incomplete initial TURBT. However, no reliable predictors have been developed to help select patient candidates who could avoid Re-TURBT in NMIBC. **Methods:** This was a blinded, observational, prospective multicenter study (NCT05112523). A total of 162 patients who underwent initial TURBT and were scheduled for Re-TURBT were enrolled in this study between June 2021 and August 2023 from four centers. Urine sample of each patient was collected prior to Re-TURBT. High-throughput sequencing of 17 genes and methylation analysis for ONECUT2 CpG sites were combined as a liquid biopsy test panel named OncoUrine. The OncoUrine test results were compared to pathological results at Re-TURBT to assess the performance in predicting residual tumor and predictive value of risk stratification. Patients who received intravesical infusion chemotherapy or BCG were followed up for recurrence analysis. **Results:** 151 patients were finally included for performance analysis. At Re-TURBT, 48 (31.8%) samples had residual tumor and 103 (68.2%) had no residual tumor. 1 Ta and 2 T1 patients were up staged to T2 at Re-TURBT. Overall, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of OncoUrine test were 77.1%, 77.7%, 61.7%, and 87.9%. Compared to OncoUrine, Cytology prior to Re-TURBT yielded a high specificity of 95.8% but lower sensitivity of 20% and combined with OncoUrine improved the sensitivity to 75.6%. In the overall OncoUrine test results, variants from 12 genes showed positive mutations. TERT, TP53, ERBB2, FGFR3, and PIK3CA were on the top 5 of the lists with other mutations from ERBB3, ERCC2, U2AF1, HRAS, KDM6A, KRAS, and ROHA. 132 were followed up with a median of 362 days (range 21 to 953). 19 patients were found recurred. The pathological results at Re-TURBT, OncoUrine, methylation and TERT results were risk stratification approaches for the recurrence analysis (positive vs. negative, $p < 0.05$). **Conclusions:** OncoUrine test after initial TURBT for NMIBC showed promise as to guide patient selection for Re-TURBT and risk stratification in the management of NMIBC. Clinical trial information: NCT05112523. Research Sponsor: None.

PEMBROBLAD: Real world effectiveness and safety of immune checkpoint inhibitors in patients with advanced urothelial carcinoma with histological variants.

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Background: A non-negligible portion of bladder cancers have non-pure UC histology; these tumors are often underdiagnosed and represent an unmet treatment need. Efficacy of immune checkpoint inhibitors (ICI) in non-pure UC remains unknown. We report preliminary data form the PEMBROBLAD study assessing ICI in pretreated mixed variants (UC-V) or pure non-UC (NUC) in real life condition. **Methods:** PEMBROBLAD is a retrospective multicenter study conducted in 24 French GETUG centers. Eligible patients had advanced UC with UC-V or NUC. All patients received ICI as a second line treatment. We excluded patients with ICI maintenance therapy. The primary endpoint was overall survival (OS); secondary endpoints included overall response rate (ORR), progression free survival (PFS), time to treatment failure (TTF) and safety. **Results:** A total of 139 patients (pts) were analyzed. Median age was 70 years (range 44-88), 70.8 % were male with ECOG PS 0/1, 2 and 3 in 57.7%, 26.6% and 10.1% of cases respectively. The most common variants of UC-V (n=96, 69.0%) were squamous cell differentiation (n=25, 26.0%), sarcomatoid (n=12, 12.5%), micropapillary (n=9, 9.3%), neuroendocrine (n=8, 8.3%), nested (n=7, 7.3%) and adenocarcinoma (n=5, 5.2%); squamous cell carcinoma (n=23, 53.4%) represented the majority of NUC (n=43, 31.0%). At data cutoff (August 15, 2023), median follow-up was 35.1 months (mo) (range 3.7-86.9). The most administered ICI was pembrolizumab in 85.6% of cases followed by durvalumab in 12.2% of cases. Median OS was 6.1 mo for all pts, 6.1 and 5.9 for UC-V and NUC respectively. In pts with UC-V and NUC, ORR was 31.2 % (n=30) and 18.6% (n=8) and DCR was 41.6% (n=40) and 23.2% (n=10) respectively. In all 139 pts, median TTF was 2.2 mo (95% CI, 0.1-50.0 mo). Serious TRAE occurred in 13 pts (9.3%). Discontinuation due to TRAEs occurred in 5.0% of pts. **Conclusions:** Our results suggest some efficacy of ICI in pretreated advanced UC-V and NUC. No new safety concerns were identified. Updated results with subgroup analysis will be reported at the meeting. Research Sponsor: None.

	Mixed UC (n =96)	Pure non UC (n=43)
Squamous cell carcinoma	25 (26.0%)	23 (53.5%)
Sarcomatoid	12 (12.5%)	
Micropapillary	9 (9.3%)	
Neuroendocrine	8 (8.3%)	8 (18.6%)
Nested	7 (7.3%)	
Adenocarcinoma	5 (5.2%)	12 (27.9%)

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

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Background: Erdafitinib (E) is a treatment option in mUCpatients with somatic FGFR2/3 GAs after progression on platinum-based chemotherapy (PBC). Enfortumab Vedotin (EV) is approved as a single agent to treat mUC patients following prior PBC and PD1/L1 inhibitors or as second-line therapy for cisplatin-ineligible patients. Retrospective studies suggest that the activity of EV is not compromised by FGFR2/3 GAs. E and EV have different mechanisms of activity, and toxicities are mostly non-overlapping. Hence, there is rationale to evaluate the feasibility of combination E + EV, to overcome the difficulties of resistance and sequencing agents in mUC patients with FGFR2/3 GAs. **Methods:** This is an ongoing, single arm, multicenter, dose-escalation and expansion study of combination E + EV evaluating the safety, tolerability, pharmacokinetics (PK), and antitumor activity in patients with mUC harboring somatic FGFR2/3 GAs who have progressed after PBC and/or PD1/L1 inhibitor therapies. Dose escalation phase aims to identify the maximum tolerable dose and recommended phase 2 dose of EV at dose levels of 1 mg/kg and 1.25 mg/kg in combination with E at 8 mg/day as shown in the table. Preliminary safety, PK, and efficacy data for Dose Level (DL) 1 and 2 are presented in this abstract. **Results:** As of data cutoff, based on 3+3 design, total 8 patients are enrolled and finished dose limiting toxicity (DLT) period (1^{st} cycle). Six patients were enrolled in DL1 with 1 DLT (skin rash) and 2 patients in DL2. The most common treatment-related adverse events (TRAE) included hyperphosphatemia (88%), mucositis (88%), hypercalcemia (75%), high AST (75%), hand foot syndrome (75%), peripheral neuropathy (75%), alopecia (63%), diarrhea (63%), hypoalbuminemia (63%) and hypomagnesemia (63%). Grade 3 TRAE included hand foot syndrome (50%), anemia (17%), rash (17%), anorexia (17%) and paronychia (17%). One patient developed grade 4 Stevens-Johnson syndrome related to EV which subsequently improved. PK data are available for all 6 subjects in DL1. The average steady-state Cmin of E and monomethyl auristatin E (MMAE) was 1430 ± 639 ng/mL and 1.4 ± 0.9 ng/mL, respectively, and the average Cmax of MMAE was 3.9 ± 0.9 ng/mL at DL1. All 8 patients are evaluable for response, and best response is partial response in all. Detailed safety and additional efficacy data will be presented. **Conclusions:** Combination E + EV is feasible and preliminarily exhibits antitumor activity. Dose escalation is ongoing to identify the MTD or recommended dose for expansion of the trial. Clinical trial information: NCT04963153. Research Sponsor: NCI-CTEP.

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

Randomized phase III clinical trial of neoadjuvant intravesical mitomycin C (MMC) treatment in patients with primary treatment-naïve vesical neoplasms: Interim analysis.

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Background: The aim of the current study is to evaluate the safety, tolerability, and efficacy of neoadjuvant MMC in patients (pts) with non-muscle invasive bladder cancer (NMIBC). **Methods:** This is a prospective phase III randomized clinical trial in pts with primary clinical diagnosis of urinary bladder cancer or secondary recurrent untreated bladder cancer since May 2022 to September 2023 (EudraCT 2021-003751-42_studio ICH-013-). Pts are randomized 1:1 to neoadjuvant MMC arm (neoA) or standard arm (StA). In the 2 weeks before scheduled TUR (day 0) neoA pts receive intravesical instillations of MMC (40 mg/40 ml saline) at day -14 and -7 and cystoscopy with a cold cup biopsy at -14. After TUR, clinical choices both in the two groups, depend on histological evaluation of the tumour and EAU guidelines. Midstream and catheter urines are collected before instillations, at day 0 and after 3 months to respectively measure the level of specific biomarker (i.e., HMGB1) and to identify the microbiota. The expression of a mitomarker is evaluated on tissue samples. The primary endpoint is to assess safety, tolerability, and efficacy of neoadjuvant MMC in reducing the recurrence rate of BC calculated as the proportion of pts who achieve a complete response (no evidence of BC after 3, 6, 12 and 24 mo). The secondary endpoint will be the analysis of the rate of grade and stage progression to MIBC in case of recurrence and the correlation with biomarkers. **Results:** The interim analysis (median follow-up 6 months) included 54 pts: 26 in the StA and 28 in the neoA. Respectively in StA and neoA mean age at TUR was 66.5 (±9.9) and 65.8 (±9.9), males were 23 (88.46%) and 24 (85.71%). No statistically significant difference was observed between groups. 5 neoA pts [17.86% (95%CI 6.06-36.89)] after instillations reported 4 different adverse reactions, grade 1 of Clavien Dindo classification. NeoA pts showed higher level of HMGB1 at day 0 and after 3 months, suggesting an increased induction of immunogenic cell death (ICD). Shotgun metagenomics on microbial DNA from catheter urine is still ongoing. In field recurrence has been observed in 1 (3.85%) StA and 2 (7.14%) neoA pts. **Conclusions:** Preliminary data show neoadjuvant MMC to be safe and well tolerated and seem to correlate with increase of HMGB1. The short follow-up and the small sample size do not allow conclusion on the efficacy. Clinical trial information: EUCTR2021-003751-42. Research Sponsor: None.

Enfortumab vedotin treatment regimens and efficacy in urothelial carcinoma: The Mayo Clinic experience.

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Background: Enfortumab vedotin (EV) is an antibody-drug conjugate recently approved to treat locally advanced or metastatic bladder cancer (la/mUC). Initial trials have shown promising response to EV in advanced urothelial cancers (UC), where prognosis is currently poor. Here, we report real-world experience using EV at a tertiary center. **Methods:** This study reports treatment details and outcomes in 92 patients (pts) that received at least one complete cycle of EV monotherapy in treatment of la/mUC. Treatment details include intent of cycle duration, 21 days (treatment on days 1 and 8) or 28 days (treatment on days 1, 8 and 15), dose reductions, and median number of cycles completed. Interruptions in treatment are reported as intentional (i.e. holding EV after achieving positive response) or unintentional (i.e. secondary to drug toxicity or other delay). Image-based best clinical response consists of progressive disease (PD), stable (SD), partial (PR), complete response (CR), and not evaluable (NE). Clinical benefit rate (CBR) is defined as either SD, PR, and CR outcomes. The Kaplan-Meier method was used to estimate overall survival (OS) and progression-free survival (PFS). **Results:** Patients mean age was 71.1 years (IQR: 66.8 - 78), 72 (79.2%) are male and 20 (20.8%) female, 89 (96.7%) pts received EV in the setting of metastatic UC, 3 (3.3%) in locally advanced UC. 13 (13.5%) pts were previously chemotherapy exposed, 9 (9.8%) were immunotherapy exposed, 60 (65.2%) were both chemo and immunotherapy exposed, and 11 (12.0%) received EV first line. 46 (50%) pts underwent 21-day treatment cycles, and 46 underwent 28-day treatment cycles. The median number of EV cycles was 3 (range 1-16) in the overall cohort, 3 in the 21-day cycle group, and 4 in the 28-day cycle group. 50 (54.3%) pts required dose reductions secondary to toxicity. 11 (12.0%) pts had planned interruptions, and 33 (35.9%) had unplanned interruptions. Best clinical response consisted of 24 (26.0%) pts with PD, 12 (13.0%) with SD, 25 (27.2%) with PR, 17 (18.5%) with CR, and 14 (15.2%) NE. CBR was 54 (58.7%) in the overall sample. CBR in the 21-day and 28-day cycle groups was identical at 27 (29.3%). EV therapy was discontinued most for cancer progression (34, 37.0%), therapy toxicity (18, 19.6%), and pt death (12, 13.0%). In 13 (14.1%) pts therapy is still ongoing. 73 (76.0%) pts had mild to moderate toxicities, and 19 (19.7%) reported severe toxicities that required hospitalization. Median OS in the total cohort was 11.01 months (95% CI: 8.51-14.6). Median PFS is 5.49 months (95% CI: 4.60-8.19). **Conclusions:** Real-world utilization of EV showed significant heterogeneity in administration patterns (21 days vs 28 days) and across a range of settings (first line, chemo exposed, IO exposed, chemo and IO exposed). Although EV has high response rates, more than $3/4^{th}$ of patients suffered mild to moderate toxicities and $1/5^{th}$ required hospitalization. Research Sponsor: None.

A randomized phase II study of atezolizumab (atezo) plus recombinant human IL-7 (CYT107) in patients with locally advanced or metastatic urothelial carcinoma.

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Background: Atezolizumab (atezo) is an anti-PD-L1 antibody that was approved for use in patients with mUC following platinum-containing regimens. IL-7 (CYT107) is a homeostatic cytokine that supports the proliferation and persistence of T cells. We hypothesized that combining CYT107 with atezo would improve responses in mUC patients. **Methods:** To test this, we performed a randomized trial (NCT03513952) comparing the combination of CYT107/atezo to atezo alone in patients with mUC previously treated with a platinum regimen. Key eligibility criteria included ECOG PS 0-2, measurable disease (RECIST 1.1), and no prior systemic immunotherapy. A safety run-in using CYT107/atezo was performed (n=7), followed by randomization 1:1 to atezo 1200 mg IV q3wks +/- CYT107 10 ug/kg IM qwk X 4. The primary endpoint was objective response rate (ORR), with secondary endpoints of clinical benefit rate, PFS, DOR, OS, and safety, with a number of exploratory correlative analyses. **Results:** A total of 47 patients were enrolled. Patient demographics between arms were well-balanced. No dose limiting toxicities (DLTs) were seen. Overall, the combination of CYT107/atezo was well tolerated compared to the atezo monotherapy arm, with overall grade 3-4 (G3-4) adverse events (AEs) occurring in 46.2% (12/26) and 63.2% (12/19) of patients, respectively. Rates of treatment-related events were: Any (80.8% vs 73.7%), G1-2 (65.4% vs 36.8%), and G3-4 (15.4% vs 36.8%) in CYT107/atezo vs monotherapy arms, respectively. Treatment-related immune-mediated AEs of any grade occurred in 50% (13/26) of patients in combination arm vs 68.4% (13/19) in monotherapy arm. 0% vs 17.6% of patients on the combination vs monotherapy arm discontinued therapy due to toxicity, respectively. ORR was 26.3% vs 23.8% in the combination vs monotherapy arm (p=0.43), respectively. Complete responses (CR) were seen in 10.5% (2/19) and 4.8% (1/21), and partial responses seen in 15.8% (3/19) and 19% (4/21) of patients in the combination vs monotherapy arms, respectively. There were no significant differences in clinical benefit rate (36.8% vs 42.9%), PFS (2.3 vs 2.2 mos), or OS (9.1 vs 10.4 mos). Rapid expansion of T cells was observed (~1.7-fold by day 8 following first dosing) in the CYT107/atezo arm only. Expansion peaked earlier for CD4s (~2-fold, day 22) and later for CD8s (~2.1-fold, day 29) and was maintained above baseline through C6D01. Detailed T cell subset pharmacodynamic data will be presented. **Conclusions:** This is the first randomized trial of atezo +/- IL-7 (CYT107) in mUC. During the trial, the FDA approval for atezo in mUC was withdrawn, which limited enrollment. However, our results show that the addition of CYT107 to atezo is safe/tolerable, with comparable toxicity profile and efficacy to monotherapy. Clinical trial information: NCT03513952. Research Sponsor: NCI/NIH; Genentech; RevImmune.

Infigratinib versus placebo in patients with resected urothelial cancer (UC) bearing FGFR3 mutation or fusion: Primary DFS analysis from the phase 3, randomized PROOF302 study.

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Background: In the subset of patients with UC bearing alterations in the fibroblast growth factor 3 (*FGFR3*) gene, targeted therapies directed at this moiety have shown substantial antitumor effect in the metastatic setting. We examine infigratinib, a potent and selective inhibitor of FGFR3, as adjuvant therapy in patients with high-risk resected UC. **Methods:** In an international multicenter phase III clinical trial, we randomly assigned patients in a 1:1 ratio to receive either oral infigratinib (125 mg) or placebo daily for 21 days of a 28-day treatment cycle, for a maximum of 13 cycles or until disease recurrence. Eligible patients had confirmed invasive UC with susceptible *FGFR3* alterations and had undergone radical surgery within 120 days of randomization. The primary endpoint of the study was centrally assessed disease-free survival (DFS), with secondary endpoints including investigator-assessed DFS, metastasis-free survival (MFS) and overall survival (OS). **Results:** Despite intensive efforts to enroll approximately 218 patients (with 822 patients consented to molecular pre-screening), only 39 patients were enrolled with 20 and 19 patients randomized to receive infigratinib and placebo, respectively. The frequency of *FGFR3* alteration was significantly lower than anticipated, occurring in only 19% of patients overall; mutations were observed in 13% of patients with lower tract UC and 30% of patients with upper tract UC. No significant differences were observed in DFS, MFS or OS, and more frequent grade 3/4 adverse events were noted in the experimental arm (35% versus 16%). No fatal adverse events were observed. **Conclusions:** Our failure to accrue sufficient patients to the current trial precludes any definitive conclusions around the role of infigratinib as adjuvant therapy for *FGFR3*-altered UC. In the process of study conduct, however, we garnered substantial insights that may aid in the development of future precision oncology trials for adjuvant UC. Clinical trial information: NCT04197986. Research Sponsor: QED Therapeutics, Inc.

Clinical outcomes of frontline GemFLP in advanced urachal and non-urachal adenocarcinomas of the urinary tract: The MD Anderson Cancer Center (MDACC) experience.

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Background: Adenocarcinomas of the urinary tract, including urachal (UA) and non-urachal (NUA) subtypes, are rare tumors. Triplet regimens combining gemcitabine, a taxane or 5-fluorouracil (5-FU)/leucovorin (L), and cisplatin (P), have been developed. **Methods:** We retrospectively reviewed records of patients receiving frontline (1L)GemFLP (Gemcitabine 200 mg/m^2 IV on days 1 and 5; 5-FU 200 mg/m^2 IV on days 1, 2, 3, 4, 5; L 10mg/m^2 IV on days 1, 2, 3, 4, 5; P 20mg/m^2 IV on days 1, 2, 3, 4, 5) in advanced UA and NUA at MDACC between 2003 and 2023. Advanced disease is defined as Sheldon stages IVA/IVB in UA and TNM stage IV in NUA. Imaging-based best overall responses (BOR) were complete (CR), partial (PR), stable (SD), progressive (PD) or non-evaluable (NE). Overall response rate (ORR) covers CR + PR, while disease control rate (DCR) covers CR + PR + SD. We report overall survival (OS) and progression-free survival (PFS) from GemFLP start. **Results:** Baseline characteristics of UA (n=40) and NUA (n=28) are in Table. In UA, bladder dome was primary location in 39 (97.5%). NUA pts had either bladder (11, 39.3%) or urethral (17, 60.7%) origin. BOR in 1L GemFLP are shown in Table. In UA, ORR is 20% and DCR is 72.5%. Median OS (mOS) is 19.8 months (95% CI: 12.2 - 30.6) and median PFS (mPFS) is 5.3 mo (95% CI: 3.1 – 6.3). In UA, pts with CR, PR, or SD have a significantly longer mOS than pts with PD [26 mo (16.2 – 35.6) vs. 7.7 mo (2.67 – 11.9), log-rank p <0.0001]. Meanwhile, in NUA, ORR is 35.7% and DCR is 75%. mOS is 12.95 mo (95% CI: 7.1-20.2) and mPFS is 5.3 mo (1.93 – 7.6). A similar significant survival benefit is seen in NUA pts with disease control versus pts with PD [17.6 mo (12.6 – 25.9) vs. 5 mo (2.63 – 7.1), p <0.0001]. Surgical consolidation was offered for 6 UA pts (3 PR, 3 SD), 3 of whom were regional N+ only, and for 4 NUA pts (1 CR, 1 PR, 2 SD) who were all regional N+ only. All except one showed residual pathological disease. **Conclusions:** 1L GemFLP is an active regimen in advanced UA and NUA, with a DCR of >70%. Pts with disease control (CR, PR, or SD) have a clear survival benefit compared to non-responders. 1L GemFLP might offer chances at surgical consolidation after disease control for pts with regional node-positive only disease, with larger cohorts needed to confirm findings. Research Sponsor: None.

Variable		UA (n=40)	NUA (n=28)
Characteristics			
Age at mets, median [ICR]		57.3 [45.4 – 62.7]	64 [59 – 67]
Race, n (%)	White	32 (80%)	18 (64.3%)
	Black	6 (15%)	7 (25%)
	Other	2 (5%)	3 (10.7%)
Prior surgery for localized disease, n (%)		22 (55%)	7 (25%)
Visceral mets at 1L GemFLP, n (%)	Any	31 (77.5%)	17 (60.7%)
	Lung	16 (40%)	8 (28.6%)
	Liver	4 (10%)	1 (3.6%)
	Peritoneum	15 (37.5%)	1 (3.6%)
	Bone	3 (7.5%)	6 (21.4%)
Nodal-only mets at 1L GemFLP, n (%)		9 (22.5%)	11 (39.3%)
Outcomes			
BOR to 1L GemFLP, n (%)	CR	0 (0%)	1 (3.6%)
	PR	8 (20%)	9 (32.1%)
	SD	21 (52.5%)	11 (39.3%)
	PD	7 (17.5%)	5 (17.9%)
	NE	4 (10%)	2 (7.1%)
Surgical consolidation after 1L GemFLP, n (%)		6 (15%)	4 (14.3%)

Efficacy and safety of disitamab vedotin combined with toripalimab as neoadjuvant treatment in patients with HER2 positive locally advanced muscle-invasive urothelial bladder cancer.

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Background: For HER2 positive muscle-invasive bladder cancer (MIBC), the efficacy of cisplatin-based NAC is unsatisfied, and adverse reactions are inevitable or even intolerable. Disitamab vedotin is an antibody-drug conjugate composed of an anti-HER2 antibody disitamab and MMAE payload. Multiple clinical studies have confirmed that promising activity in HER2-positive locally advanced or mUC patients。This study aims to evaluate the safety and efficacy of disitamab vedotin, and toripalimab as a novel neoadjuvant treatment combination in patients with HER2 positive locally advanced MIBC. **Methods:** In this Study, Platinum intolerance and pathological andimaging diagnosed cT2-4bN0M0 MIBC patients with HER2 positive (HER2 IHC2+ or HER2 IHC3+) received 3 cycles toripalimab (200mg, iv, D1, Q2W) combined with disitamab vedotin (2mg/kg, iv, D1, Q2W). The primary endpoint was pCR, and the secondary endpoints included PFS, OS, and safety. **Results:** From July 2023 to Sep 2023, 12 patients were enrolled. The median age was 68 (55-82) years . By the data cut off in August 2023, the primary end point pCR was 80% (8/10). Median follow-up time was 4.2 (2.2-8.45) month. The median overall survival (OS) was not reached , ORR was100%. In terms of safety, the treatment-related adverse events (TRAEs) of any grade occurred in ten patients (83.3%), and the most common TRAEs were nausea (58.3%), followed by alopecia (33.3%), diarrhea (16.7%) and Cardiac tachycardia (8.3%). most of which are grade 1-2. Grade 3 TRAE is Cardiac tachycardia and occurred in one patient. No grade 4 and 5 TRAEs were observed. **Conclusions:** From July 2023 to Sep 2023, 12 patients were enrolled. The median age was 68 (55-82) years . By the data cut off in August 2023, the primary end point pCR was 80% (8/10). Median follow-up time was 4.2 (2.2-8.45) month. The median overall survival (OS) was not reached, ORR was100%. In terms of safety, the treatment-related adverse events (TRAEs) of any grade occurred in ten patients (83.3%), and the most common TRAEs were nausea (58.3%), followed by alopecia (33.3%), diarrhea (16.7%) and Cardiac tachycardia (8.3%). most of which are grade 1-2. Grade 3 TRAE is cardiac tachycardia and occurred in one patient. No grade 4 and 5 TRAEs were observed. Research Sponsor: None.

Oral APL-1202 in combination with tislelizumab as neoadjuvant therapy in patients with muscle-invasive bladder cancer (MIBC): Interim analysis of ANTICIPATE phase II trial.

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Background: APL-1202 (nitroxoline) is a reversible and orally available MetAP2 inhibitor with anti-angiogenic and anti-tumor activities. Single-agent neoadjuvant programmed death 1 (PD-1) antibodies achieve pathological complete responses in a subset of patients (pts) with MIBC. APL-1202 and PD-1 antibody combination therapy demonstrates synergistic effects in several model systems of cancer, including bladder cancer. We hypothesized that APL-1202, in combination with tislelizumab, a humanized IgG4 anti-PD-1 antibody, may be an effective neoadjuvant therapy in MIBC. **Methods:** This is a prospective multicenter randomized phase II trial for pts with newly diagnosed MIBC for whom radical cystectomy (RC) is planned, and who are cisplatin ineligible or refuse cisplatin based neoadjuvant chemotherapy. Eligible pts are randomly assigned to group 1 (APL-1202 plus tislelizumab) or group 2 (tislelizumab), with randomization stratified by PD-L1 expression. Neoadjuvant treatment is administered every 3 weeks for 3 cycles. The primary endpoint is pathological complete response (pCR, pT0N0) rate. A Simon's 2-stage design is employed with planned interim analyses after 18 evaluable pts in group 1 and 14 evaluable pts in group 2. **Results:** 42 pts have enrolled and results for 32 evaluable pts for stage 1 of the 2-stage design are reported. Radical cystectomy was completed in 18/18 pts in group 1 and 13/14 pts in group 2; 1 patient who could not undergo surgery due to disease progression and 10 pts refused RC. The 32 evaluable pts consisted of 11/18 (61%) and 10/14 (72%) cT2, and 6/18 (33%) and 2/14 (14%) cT3, and 1/18 (6%) and 2/14 (14%) cT4a in group 1 and 2, respectively. PD-L1 expression was assessed using the VENTANA PD-L1 (SP263) Assay; 8/18 (44%) pts in group 1 and 7/14 (50%) in group 2 was positive. The pathological response was shown in the table. Treatment emergent adverse events (TEAEs) were reported in 17 (94.4%) pts in group 1 and 11 (78.6%) in group 2; most common (≥ 10%) TEAE of CTCAE grade ≥ 3 were anaemia (4, 22.2%), lymphocyte count decreased (3, 16.7%) in group 1 and intestinal obstruction (3, 21.4%) in group 2. AEs led to drug discontinuation in 3 (16.7%) pts in group 1 (acute kidney injury, anaemia, hepatic function abnormal) and 2 (14.3%) in group 2 (immune hyperthyroidism, COVID-19), and no treatment-related AEs led to death. **Conclusions:** The pCR rates in both group 1 (APL-1202 plus tislelizumab) and group 2 (tislelizumab) exceeded thresholds to trigger expansion to stage 2 of the 2-stage design. The activity and safety of neoadjuvant APL-1202 plus tislelizumab support further evaluation of this novel regimen (NCT04813107). Clinical trial information: NCT04813107. Research Sponsor: None.

Pathological response to treatment.

Response	Group 1 (N=18) (APL-1202+Tislelizumab)	Group 2 (N=14) (Tislelizumab)
pCR	7/18 (39%)	3/14 (21%)
<pT2N0	8/18 (44%)	3/14 (21%)

Avelumab or pembrolizumab: Which is the better subsequent treatment in patients with advanced urothelial carcinoma who did not show progression after 4 cycles of first line chemotherapy?

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Background: In platinum eligible patients with advanced urothelial carcinoma (UC), there are two treatment options if they did not show progression after 4 cycles of first line chemotherapy. One is switching to avelumab maintenance therapy and the other is pembrolizumab after the disease progression on first line chemotherapy. However, there is no data witch treatment strategy demonstrate better survival. This study aimed to compare the efficacy between avelumab and pembrolizumab after first line chemotherapy without disease progression. **Methods:** We retrospectively reviewed patients with advanced UC who received avelumab or pembrolizumab as subsequent therapy following first line platinum-based chemotherapy between March 2018 and Jun 2023. In patients who receive pembrolizumab, only patients who did not show progression after 4 cycles of first line chemotherapy were included in the study cohort. The oncological outcomes were compared between the patients who received avelumab and pembrolizumab. **Results:** Thirty-three and 100 patients received avelumab and pembrolizumab during study periods, respectively. Among 100 patients who received pembrolizumab, 14 patients did not show progression during 4 cycles of first line chemotherapy. Median 4 and 6 cycles of first line chemotherapy were performed in patient treated with avelumab and pembrolizumab, respectively. All patients treated with pembrolizumab showed disease progression after 1st line chemotherapy. With the median follow-up of 16.7 months, progression was observed in 19 (57%) and 12(86%) patients in avelumab and pembrolizumab group, respectively. Among the patients with progression, all patients had treated with avelumab received subsequent treatment mainly enfortumab vedotin. However, only 2 patients (17%) had treated with pembrolizumab received subsequent treatment and the other patients were not candidate of additional treatment due to poor PS or cachexia. Although median progression free survival from starting first line chemotherapy was shorter in patients with avelumab compared to pembrolizumab (9.7 vs. 19.9 months, P=0.06), median OS was longer in patients with avelumab (40.9 vs. 24.9 months, P=0.34). **Conclusions:** In patients who did not show progression after 4 cycles of first line chemotherapy, avelumab maintenance therapy might be a better treatment option with longer overall survival compared to pembrolizumab.
Research Sponsor: None.

Clinical impact of C-reactive protein flare response in patients with advanced urothelial carcinoma who received pembrolizumab.

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Background: C-reactive protein (CRP) has been reported as one of the useful predictive markers in patients with advanced urothelial carcinoma (UC). Not only baseline revel, kinetics of CRP during medical treatment also has been demonstrated. However, there are extremely limited data on temporary elevated CRP levels followed by decreasing below baseline (CRP flare response) after administration of immune checkpoint inhibitors. The aim of this study was to clarify the clinical significance of CRP flare response after administering pembrolizumab in patients with advanced UC. **Methods:** We retrospectively reviewed patients with advanced UC who consecutively received pembrolizumab as second-line or later therapy between March 2018 and January 2023 at one academic center and six general hospitals. Patients were categorized into 3 groups according to early CRP kinetics: flare-responder (CRP levels had increased to more than double from baseline within 1 month after pembrolizumab administration (CRP flare) and decreasing to below-baseline levels within 3 months); responder (CRP levels decreased ≥30% from baseline within 3 months without CRP flare); non-responder (the remaining patients). Tumor responses, overall survival (OS), progression-free survival (PFS), and adverse events (AEs) were compared among the groups. **Results:** A total of 97 eligible patients, 15, 25, and 57 patients were classified into flare-responder, responder, and non-responder group, respectively. Objective response rates of flare-responder (43%) and responder (52%) were higher than that of non-responder groups (17%). Median follow-up was 7.8 months. Progression and death were observed in 83 and 70 patients during follow-up, respectively. Median OS was 19.8, 15.2, and 7.8 months in the flare-responder, responder, and non-responder group, respectively (P= 0.03). Furthermore, Median PFS was 8.1, 6.3, and 2.7 months in the flare-responder, responder, and non-responder group, respectively (P= 0.006). In multivariate analysis, CRP-flare response was a significant favorable predictive factor associated with OS. The patients who developed any grade AEs were 33, 40, 20.7% in the flare-responder, responder, and non-responder group, respectively (P= 0.16). Similarly there were no significant differences in occurrence of severe AEs (≥Grade 3). **Conclusions:** CRP flare response was observed in 15% of patients with advanced UC who received pembrolizumab and favorable oncological outcomes were observed in these patients. CRP-flare might be a promising predictive and prognostic marker in patients with advanced UC who underwent pembrolizumab therapy. Research Sponsor: None.

Urinary minimal residual disease detection predicts recurrence in BCG-unresponsive NIMBC and quantifies molecular response to nadofaragene firadenovec.

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Background: Urinary minimal residual disease (uMRD) profiling uses next-generation sequencing to identify mutations associated with urothelial carcinoma and can be used to predict recurrence and assess response to therapy. Nadofaragene firadenovec is a novel intravesical therapy recently approved for BCG-unresponsive non-muscle-invasive bladder cancer (NMIBC). We evaluate the utility of uMRD to identify molecular response to Nadofaragene in patients with high-grade (HG) BCG-refractory or relapsed NMIBC. **Methods:** This was an open-label, multicenter, parallel-arm, phase II study (NCT01687244) of 43 patients with BCG-unresponsive NMIBC who received intravesical nadofaragene. The primary endpoint was 12-month HG-recurrence-free survival (RFS). All patients who received at least one dose were included in the uMRD analysis. Urine samples were collected prior to induction and at 3 months. uMRD testing was done using the UroAmp MRD assay, which identifies single-nucleotide variants, copy-number variants (CNVs), insertion-deletions, copy-neutral loss of heterozygosity, microsatellite instability, and aneuploidy. **Results:** Among evaluable patients (n=35), initial pathological stages were Ta (n=3), T1 (n=9), and Tis (n=23), with concomitant CIS in six patients. In pre-treatment urine (n=32), TP53, TERT, PIK3CA, ARID1A, PLEKHS1, ELF3, and ERBB2 were among the most prevalently mutated genes. Most CNVs occurred in SOX4 and NIT1. uMRD identified patients with high (72%) and low (28%) recurrence risk in both pre- and post-induction collections. At 12 months, post-induction RFS rate was 100% for low-risk and 38% for high-risk patients (P = 0.038, log-rank test). Pre-induction RFS was 56% for low-risk and 22% for high-risk (P = 0.097, log-rank test). Using matched pre- and post-induction urine (n=15), quantitative drug response was measured and patients categorized as MRD Negative (7%), MRD Complete Responder (13%), MRD Partial Responder (27%), MRD Stable (20%), or MRD Refractory (33%). Recurrence correlated broadly with response groups: MRD Negative and Complete Responder groups did not recur on study, while 7 of 12 patients in the other groups recurred. **Conclusions:** uMRD enables quantitative assessment of molecular response to drug treatment. uMRD-determined pre-treatment disease burden assessment can support stratification of control and intervention arms in future treatment trials. Research Sponsor: None.

Neoadjuvant combined chemotherapy and immunotherapy for upper tract urothelial carcinoma: Preliminary results from a phase II study.

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Background: Upper Tract Urothelial Carcinoma (UTUC) presents a challenging prognosis even after Radical Nephroureterectomy (RNU), and postoperative renal insufficiency further limits the options for adjuvant therapy. The efficacy of neoadjuvant chemotherapy for UTUC remains uncertain as past studies have not shown satisfactory results and have mostly been retrospective. There is an urgent need for a more promising regimen. This phase II study aims to investigate the efficacy and safety of a combination of chemotherapy (Gemcitabine/Cisplatin) and PD-1 inhibitor (Toripalimab) as neoadjuvant treatment (NT) in UTUC patients. **Methods:** We planned to enroll 34 UTUC patients with either cT1N0M0 (high grade) or cT2-3N0M0, confirmed by ureterorenoscopy biopsy and imaging. The treatment regimen included three or four cycles of NT (Gemcitabine, 800mg/m^2, days 1 and 8/Cisplatin, 60mg/m^2, day 1/ Toripalimab, 240mg, day 1 of a 21-day cycle), followed by RNU and pelvic lymphadenectomy. The primary outcome was the pathological complete response (pCR) rate, with secondary outcomes including significant downstaging (≤pT1) rate, disease control rate (DCR), and safety. **Results:** To date, 17 patients have been accrued since August 1st, 2020, and recruitment is ongoing. Fifteen patients have completed treatments and were preliminarily analyzed, with two patients still undergoing treatment. The median age was 66.0 years, with 53.3% being male. The majority of patients had unifocal tumors, with a median maximum diameter of 2.8cm (0.4-5.8). All patients experienced obstructed hydronephrosis. Clinical T staging was confirmed by multi-parameter MRI, indicating two T2 and thirteen T3 patients. Ureterorenoscopy biopsy revealed 13 high-grade and two low-grade urothelial carcinoma patients. All patients were classified as high-risk UTUC. Twelve patients completed 4 cycles, and three underwent 3 cycles. The median interval time from initiation of NT to RNU and from the end of NT to RNU was 18.3 (11.4-22.7) weeks and 6.3 (0.1-11.6) weeks respectively. The pCR rate was 20.0% (3/15), the ≤pT1 rate was 53.3% (8/15), and the DCR was 100%. No grade 4-5 chemotherapy-related adverse events were recorded, but 26.7% (4/15) experienced grade 2 myelosuppression, 20% (3/15) grade 3, and 6.7% (1/15) grade 4. Two patients experienced immune-related adverse events after 4 cycles, including hypothyroidism (grade 2) and adrenal insufficiency (grade 2). No surgery-related complications or readmissions within one month were reported. With a median follow-up of 25.6 months, all patients remained alive and tumor-free. **Conclusions:** Preliminary analyses suggest that the combination of chemotherapy and a PD-1 inhibitor as NT exhibits promising pCR rate for UTUC. The treatment was manageable in terms of safety, with immune-related adverse events potentially leading to prolonged treatment periods. Clinical trial information: NCT04099589. Research Sponsor: 2021-I2M-1-033.

GCISAVE: A non-comparative randomized phase II study of combination of gemcitabine cisplatin (GCis) +/- avelumab (A) in 1st line treatment for locally advanced or metastatic urothelial bladder carcinoma (MUBC)—GETUG AFU V07.

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Background: GCis is the standard 1st line of MUBC. Immune Checkpoint Inhibitor (ICI) is indicated as maintenance with avelumab (A), in patients (pts) with objective response or stable disease after chemotherapy, or as 2ndline with Pembrolizumab, in case of disease progression. Survival improvement of combining ICI to GCis still remains under investigation. GCISAVE evaluates the efficacy and safety of combining avelumab (A) with GCis in 1st line treatment. **Methods:** GCISAVE is a prospective multicenter randomized (2:1) non-comparative open-label phase II study, assessing the efficacy and safety of 6 cycles of GCis +/- A on a two-stage Bryant-Day design. Pts fit for cisplatin received GCis (G 1000 mg/m2, D1,D8; Cis 70 mg/m2, D1) +/- A (10 mg/kg, D1), every 3 weeks. Stratification was on centre, Karnofsky and visceral vs. non-visceral metastases. Two co-primary endpoints were the objective response rate (ORR) at week 18 (target≥ 60%) and the incidence of grade ≥3 treatment related adverse events (TRAE) (target<30%). Secondary objectives included: duration of response, 18 month PFS and OS; describing ORR according to the expression of PD-L1, immune infiltrate population and proteomics. **Results:** Between 11/2017 and 11/2020, 65 pts have been included, 42 (GCis+A) and 23 (GCis). Study was stopped prematurely due to the approval of A as maintenance treatment. Clinical characteristics were well balanced. 20 pts (47.6 %) in GCis + A arm and 7 pts (31.8 %) in GCis arm achieved 6 cycles with cisplatin : male (83.3 and 81.8%), median age (68 (62-71) and 67(56-72) yo), M1 stage for 76.2 and 77.3% respectively. 18 pts (42.9 %) in GCis + A and 13 pts (59.1 %) in GCis crossed to carboplatin. At week 18, ORR was 79.5% in the (GCis+A), including 15% Complete Response (RC) (39 pts evaluable), and 59.1% (GCis) arm (22 pts evaluable) respectively. TRAE were reported in 11 pts (26.2 %) in GCis+A arm. An oncoprot signature was obtained for CR and Partial Response compared to Progressive Disease (PD). **Conclusions:** GCis+A achieved the predefined target values with ORR ≥60% and ≤30% of SAE in 1st line treatment of MUBC. An oncoprot panel seemed to be correlated to PR, CR vs. PD. Clinical trial information: NCT03324282. Research Sponsor: None.

Validity of renal function eligibility criteria for cisplatin-based chemotherapy for patients with urothelial carcinoma.

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Background: The eligibility criteria of renal function in cisplatin (CDDP) -based chemotherapy for urothelial carcinoma has generally been a creatinine clearance (CCr) ≥ 60 (mL/min) without adjusting for body surface area (BSA). While CDDP dosage is determined by body surface area, the use of CCr (mL/min) without correction for body surface area as a criterion for cisplatin eligibility may lead to CDDP overdose, especially in obese patients with borderline renal function. CCr with BSA modification (CCr mL/min/1.73 ㎡) may be more appropriate than without BSA modification for assessing renal function in patients with nonstandard body mass. **Methods:** This retrospective analysis included 82 patients who received CDDP-based chemotherapy as primary systemic treatment for urothelial carcinoma at Nagoya University in the past 10 years. For all patients, CDDP eligibility was determined by CCr mL/min by 24-hour urine collection, and the inclusion criteria for this study were CCr < 80 mL/min. To identify the possibility of a gap between CCr mL/min and CCr mL/min/1.73 ㎡ resulting in cisplatin overdose unit organ function, ΔCCr (difference between CCr mL/min and CCr mL/min/1.73 ㎡) and CDDP/CCr (actual dose of CDDP mg per unit CCr mL/min) were calculated and compared between the obese and standard-body groups. In addition, we compared the incidence of CTCAE Grade ≥3 adverse events (AEs) and the objective response rate (ORR) to chemotherapy in the two groups. In accordance with Japanese standards, BMI ≥ 25 was defined as obese patients. **Results:** There were no significant differences in patient background between the obese and standard groups in terms of age, gender, cancer type and status, and CDDP dose per unit BSA. CCr mL/min/1.73m2 was similar between the two groups, whereas CCr mL/min was significantly higher in the obese group, which resulted in a significantly higher ΔCCr in the obese group. In addition, CDDP/CCr was also greater in the obese group. **Conclusions:** The results of the current study suggest that the application of CCr mL/min to the assessment of renal function for CDDP eligibility may lead to CDDP overdosing, especially in obese patients with borderline renal function. Further larger studies are warranted to clarify whether or BSA correction should be applied to assess renal function for CDDP eligibility, since the method for assessing renal function may affect the occurrence of AEs and the efficacy of chemotherapy. Research Sponsor: None.

A meta-analysis assessing objective response rates with first-line systemic treatment options in locally advanced/metastatic urothelial carcinoma.

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Background: Immunotherapy combined with chemotherapy (IO/C) as the first-line management of locally advanced or metastatic urothelial carcinoma (LA/mUC) has been investigated in multiple trials with conflicting outcomes. Therefore, we conducted a meta-analysis of available trials to compare objective response rates (ORR) of this combination regimen, both in overall and in cisplatin-ineligible populations. **Methods:** EMABSE and MEDLINE were searched from 2000 through July 20th, 2023, to identify phase II and III clinical trials assessing IO, C or both in LA/mUC. Main outcome of interest was objective response rates (ORR) as defined in the included trials. An inverse variance random-effects meta-analysis was performed to estimate pooled ORR using the restricted maximum likelihood estimation method. Subgroup differences were assessed among IO/C, IO alone, and C alone. The threshold for statistical significance was established at 0.1. **Results:** Of 5975 citations identified, a total of 26 trials with a total of 4,628 participants were included in this systematic review. In the overall group, the ORR in IO/C trials (5 trials, 1,236 patients) was 44.70% (95% CI: 21.88%- 70.0%). In IO trials (7 trials, 2,189 patients), ORR was 23.68% (19.55%- 28.36%) and in C trials (26 trials, 4,628 patients) was 43.46% (37.43%-49.68%]). In the cisplatin-ineligible group, the ORR in IO/C trials (2 trials, 240 patients) was 60.06% (33.38%-81.86%), in IO trials (6 trials, 1,103 patients) was 26.15% (23.01%; 29.56%), and in C trials (8 trials, 767 patients) was 42.45% (35.67%-49.52%). In terms of subgroup differences, the difference in ORR was statistically significant between IO/C and IO trials (p= 0.0844) and between IO and chemotherapy trials (p< 0.0001) in the overall population. Similarly, we found a statistically significant difference in ORR between IO/C and IO (p= 0.0108) and between IO and chemotherapy trials (p< 0.0001) in the cisplatin-ineligible population. No statistically significant differences were observed between IO/C and C alone. **Conclusions:** First-line IO/C may achieve a better objective response compared to IO alone in patients diagnosed with locally advanced/metastatic UC. Although, there appears to be a trend of greater benefit with IO/C compared to C alone, the difference was not statistically significant. The results will be updated as soon data from new trials (CheckMate 901 and EV 302) becomes available which could offer new insights. Research Sponsor: None.

ORR (95%CI)	IO/C	IO alone	C alone
Overall population	44.70% [21.88%- 70.0%]	23.68% [19.55%- 28.36%]	43.46% [37.43%-49.68%]
Cisplatin ineligible population	60.06% [33.38%-81.86%]	26.15% [23.01%; 29.56%]	42.45% [35.67%-49.52%]

Effect of type of antibiotics (Abx) on outcomes with immune checkpoint inhibitors (ICIs) in patients (pts) with metastatic urothelial carcinoma (mUC) in a real-world setting.

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Background: Use of Abx was associated with worse overall survival (OS) and progression-free survival (PFS) in our real-world cohort of mUC pts treated with ICI. (ASCO 2023). We now report the effect of type of Abx on ICI outcomes. **Methods:** In our cohort of 335 pts with mUC treated with ≥2 cycles of ICI with atezolizumab (A) or pembrolizumab (P) at CCF between 2015 and 2023, Abx class used in at least 20 pts was included. PFS and OS were calculated using Kaplan-Meier method, outcomes compared using log-rank testing and multivariate (MVA) Cox regression method. **Results:** Of 335 pts, 26.27% received A and 73.73% received P. Median follow-up was 26.8 mos. Details of type of Abx (cephalosporins (CPH), fluoroquinolones (FQ), penicillins (PCN) and trimethoprim-sulfamethoxazole (TMP-SMX), timing (30 or 60 (d) pre or post ICI start) and OS/PFS are shown in the Table. On MVA Cox regression analysis, Abx use within 60 (d) before ICI start was associated with worse OS (10.97 vs 16.03 mos.; (HR) 1.6 [1.2 -2.1], p=0.0004). Abx use within 30 (d) post ICI was associated with worse OS (6.9 vs 14.39 mos, p=0.008). Individual Abx and effect on OS and PFS are shown in Table. On MVA Cox regression analysis, Abx use within 60 (d) post ICI start was associated with worse PFS (3.12 vs 5.67 mos., HR 1.4; p=0.015). **Conclusions:** In our large cohort of pts with mUC treated with ICI, Abx PCN, CPH and FQ, within 30 and 60 (d) prior to starting ICIs demonstrated worse OS, Abx used after 30 and 60 (d) of ICI demonstrated worse OS and PFS, especially with CPH and PCN but not FQ. These findings have the potential to influence clinical practice, including using a higher threshold for prescribing antibiotics to pts with mUC when planned for or on ICI and the choice of Abx used. Research Sponsor: None.

	60 days before ICI			30 days before ICI			30 days after ICI			60 days after ICI		
	N (pts)	OS (mos.; p-value)	PFS (mos.; p-value)	N (pts)	OS (mos.; p-value)	PFS (mos.; p-value)	N (pts)	OS (mos.; p-value)	PFS (mos.; p-value)	N (pts)	OS (mos.; p-value)	PFS (mos.; p-value)
Abx vs no Abx	82 vs 124	10.97 vs 16.03; p=0.001	4.25 vs 5.65; p=0.006	35 vs 171	9.46 vs 14.52; p=0.004	3.52 vs 5.29; p=0.393	18 vs 188	6.9 vs 14.39; p=0.008	2.99 vs 5.29; p=0.001	54 vs 152	10.87 vs 15.05; p=0.066	3.12 vs 5.67 mos., p=0.006
FQ vs no FQ	37 vs 169	10.97 vs 14.49; p=0.05	4.21 vs 5.19; p=0.126	18 vs 188	6.62 vs 14.39; p=0.011	3.52 vs 5.29; p=0.138	13 vs 193	11.47 vs 13.96; p=0.441	6.23 vs 4.86; p=0.913	22 vs 184	14 vs 13.77; p=0.834	3.25 vs 5.06; p=0.306
PCN vs no PCN	31 vs 175	10.32 vs 14.46; p=0.007	3.55 vs 5.34; p=0.096	21 vs 185	9.66 vs 14.46; p=0.021	3.42 vs 5.29; p=0.421	13 vs 193	5.19 vs 14.39; p=0.001	2.73 vs 5.29; p=0.027	24 vs 182	5.98 vs 14.46; p=0.002	2.73 vs 5.39; p=0.031
CPH vs no CPH	37 vs 159	10.68 vs 14.55; p=0.047	4.58 vs 5.29; p=0.029	21 vs 185	10.41 vs 14.42; p=0.007	4.67 vs 5.06; p=0.075				23 vs 183	5.11 vs 14.39; p=0.047	3.06 vs 5.32; p=0.021
TMP-SMX vs no TMP-SMX	9 vs 197	5.06 vs 14.39; p=0.003	2.73 vs 2.73; p=0.014									

Safety of intraoperative tranexamic acid use on the risk of venous thromboembolism (VTE) in patients undergoing robotic assisted radical cystectomy (RARC).

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Background: Perioperative blood transfusion is associated with an increased risk of adverse events and tranexamic acid (TXA) use has been proposed to decrease the need for perioperative blood transfusion. Herein, we seek to investigate the impact of intraoperative TXA on perioperative risk of VTE in a subset of patients who underwent robotic-assisted radical cystectomy (RARC) for bladder cancer. **Methods:** We queried the prospectively maintained Mayo Clinic Radical Cystectomy registry and identified patients who underwent RARC between 2004-2021 and received TXA intraoperatively. In univariable and multivariable analyses, we investigated factors associated with bleeding and VTE within 30 days post-operatively. **Results:** Of 2862 patients, we identified 94 patients who received TXA (IV) intraoperatively (Group A) and were propensity score matched 1:1 for age, neoadjuvant chemotherapy, pT stage, pN stage, and preoperative hemoglobin with a group who did not receive TXA; 38 patients (Group B). In univariable and multivariable models, use of TXA has no statistically significant impact on patient's risk of bleeding or VTE. In a univariable model, number of positive lymph nodes and extent of lymph node dissection were associated with increased risk of VTE (Table 1). **Conclusions:** In our study, use of TXA in patient's undergoing RARC was safe and was not associated with increased risk of VTE. Research Sponsor: None.

Univariable (A) and multivaraible (B) analyses of factors impacting patient's risk of VTE.

A) Effect	Estimate	95% Confidence Limits		P value
Comorbid DM	0.32	0.04	2.563	0.28
Comorbid CHF	2.511	0.245	25.717	0.44
Comorbid MI	1.364	0.274	6.799	0.70
Comorbid Renal disease	0.646	0.136	3.061	0.58
Tranexamic acid use	1.244	0.375	4.13	0.72
pT2 vs pT0	0.986	0.153	6.367	0.99
pT34 vs pT0	3.967	0.92	17.098	0.06
pTa-T1 vs pT0	1.162	0.243	5.565	0.85
Node positive (ref=neg/x)	3.495	1.123	10.877	0.03
Neo Adj Chemo	0.456	0.139	1.498	0.20
Continent conduit (ref=incontinent)	0.799	0.211	3.018	0.74
Number of Lymph nodes dissected	1.033	1.003	1.064	0.03
B) Effect	**Estimate**	**95% Confidence Limits**		**P value**
Comorbid DM	0.25	0.019	3.334	0.29
Comorbid CHF	4.148	0.161	106.579	0.39
Comorbid MI	1.896	0.314	11.458	0.49
Comorbid Renal disease	0.466	0.072	3.018	0.42
Tranexamic acid use	1.4	0.354	5.545	0.63
pT2 vs pT0	0.667	0.08	5.529	0.71
pT3-4 vs pT0	2.549	0.362	17.952	0.35
pTa-T1 vs pT0	1.204	0.215	6.743	0.83
Node positive (ref=neg/x)	1.766	0.343	9.105	0.50
Neo Adj Chemo	0.765	0.191	3.07	0.71
Continent conduit (ref=Incontinent)	0.735	0.145	3.734	0.71
Number of Lymph nodes dissected	1.027	0.988	1.068	0.18

Impact of intraoperative tranexamic acid use on overall survival and cancer specific survival in patients undergoing radical cystectomy.

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Background: Perioperative blood transfusion has been reported in up to 60% of patients undergoing RC. Unfortunately, perioperative blood transfusion in patient undergoing RC has been associated with poor oncological outcomes. Tranexamic acid (TXA) use has been proposed to decrease the need for perioperative blood transfusion. Here we seek to investigate the impact of intraoperative TXA on survival outcomes in patients undergoing radical cystectomy (RC) for bladder cancer. **Methods:** We queried the prospectively maintained Mayo Clinic Radical Cystectomy registry and identified all RC performed for bladder cancer between 1990-2021. Primary outcomes were patient's overall survival and cancer specific survival among patients who received TXA versus patients who did not receive TXA. **Results:** Among 2929 patients who underwent RC in our institution between 1990-2021, 468 received TXA (IV) intraoperatively (Group A) and were propensity score matched 1:1 for age, neoadjuvant chemotherapy, adjuvant chemotherapy, pT stage, pN stage, and preoperative hemoglobin with a group who did not receive TXA (Group B, n= 468). At 8 years followup, 61% of patients who received TXA were alive versus 46% of patients who did not receive TXA. In univariable and multivariable analyses of factors associated with CSS (Table1), node positive disease, pT2-T4, peri-operative blood transfusion were associated with poor survival outcomes. While use of TXA was associated with improved CSS outcomes. **Conclusions:** In our study, TXA use in patients undergoing radical cystectomy was associated with decreased risk or peri-operative transfusion, improved patient's overall survival, and cancer specific survival. We can't explain the biological rational for improved survival however these findings warrant further prospective investigation. Research Sponsor: None.

Univariable and multivariable cox-regression analysis of factors impacting cancer specific survival (Death from bladder cancer).

	Univariable Analysis			Multivariable Analysis		
Variable	**Odds Ratio**	**95% CI**	**P**	**Odds Ratio**	**95% CI**	**P**
Age	0.99	0.97-1.0	0.09	0.98	0.96 – 0.99	0.01
pT						
- pTa-T1 vs pT0	1.06	0.68 – 1.67	0.80	1.10	0.69 – 1.77	0.67
- pT2 vs pT0	2.32	1.42 – 3.80	0.00	2.39	1.41 – 8.06	<0.001
- pT3-4 vs pT0	5.22	3.36 – 8.10	<0.0001	4.92	3.00 – 7.97	<0.001
pN+	3.38	2.31 – 4.95	<0.0001	2.90	1.71 – 4.90	<0.001
Neoadjuvant chemo	1.25	0.91 – 1.71	0.16	1.10	0.76 – 1.60	0.61
Adjuvant chemo	1.69	1.01 – 2.83	0.04	0.46	0.24 – 0.92	0.03
Use of TXA	0.33	0.24 – 0.45	<0.0001	0.30	0.21 – 0.43	<0.0001
Perioperative blood transfusion	2.35	1.75 – 3.18	<0.0001	1.89	1.35 – 2.64	0.00

Clinical efficacy of enfortumab-pembrolizumab combination therapy in locally advanced/metastatic urothelial carcinoma (UC): A real-world experience.

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Background: The FDA approval of enfortumab (EV) and pembrolizumab (Pembro) combination therapy as a first-line treatment for cisplatin-ineligible patients with locally advanced/metastatic urothelial carcinoma (la/mUC) was based on the EV-103 trial. We aim to assess the clinical response rate of this combination therapy in our institution's patients with locally advanced and metastatic UC. **Methods:** This retrospective cohort study included 20 patients diagnosed with locally advanced/metastatic UC(la/mUC) who were treated with EV-Pembro combination for at least 2 cycles, from June 2022 to August 2023 at the Mayo Clinic. Patients who were treatment naïve or who progressed one or more lines of therapy were included in the study cohort. Main outcome of interest included imaging-based best overall response rate in terms of complete (CR) and partial (PR) response, stable disease (SD), and progressive disease (PD). **Results:** Out of 20 patients, the number of males and females were 16 (80%) and 4 (20%) respectively; the median age was 77 years (IQR: 51-92). 3 (15%) of patients had involvement of upper urinary tract disease along with bladder cancer. The common sites of visceral metastasis at the time of initial presentation include liver 2(10%), lung 6(30%) and lymph nodes12(60%). Common toxicities of this regimen included rash, pruritis, peripheral neuropathy, fatigue, transaminitis, dysgeusia, and diarrhea. The treatment was stopped in 10 (50%) patients due to completion of planned therapy (achieved CR or proceeded with resection of residual disease) (30%), 5 patients due to progression (50%), 1 patient due to therapy side effects (10%) and in 1 patient due to death (10%). The objective response was 45% (N =9); 5 (25%) had PR, and 4 (20%) had CR. A total of 2 (10%) had SD while 2 (10%) experienced PD. Histological correlation with clinical benefit is shown in the table. **Conclusions:** EV-Pembro combination therapy shows promising responses in patients who have progressed after previous lines of therapy, consistent with previously published data on EV 201 in small cohorts. However, ongoing expansion of this cohort and data from larger studies will help further elucidate survival benefits and their correlation with genetic testing. Research Sponsor: None.

Clinical benefit based on histological subtype.

Histology	Partial Response N(%)	Complete Response N(%)	Stable Disease N(%)	Progressive Disease N(%)
Pure Urothelial carcinoma	2(40)	2(40)	1(50)	0
Urothelial carcinoma with mixed histology	3(60)	3(60)	1(50)	2(100)

RC48-ADC versus BCG in adjuvant treatment of high-risk non-muscle-invasive bladder cancer with HER2 over-expression: A real-world retrospective study.

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Background: Bladder cancer ranks as the tenth most prevalent malignancy globally, with non-muscle invasive bladder cancer (NMIBC) accounting for approximately 75% of cases. Patients diagnosed with high-risk NMIBC (HR-NMIBC) face a grim prognosis, characterized by a 5-year disease progression rate of up to 40%. Currently, the standard treatment for HR-NMIBC involves transurethral resection of bladder tumor (TURBT) followed by adjuvant intravesical Bacillus Calmette-Guérin (BCG) therapy. However, BCG infusion therapy is associated with prolonged duration, substantial costs, and a high frequency of toxic side effects. RC48-ADC, a novel humanized anti-HER2 antibody conjugated with monomethyl auristatin E, has shown promising efficacy with a manageable safety profile in patients with locally advanced or metastatic urothelial carcinoma (mUC) in a Phase II clinical trial (NCT03507166). Therefore, investigating the therapeutic potential of RC48-ADC in HR-NMIBC patients holds significant clinical importance. **Methods:** We conducted a retrospective analysis on patients diagnosed with HR-NMIBC exhibiting HER2 overexpression (≥ HER2 2+) who underwent adjuvant therapy with either RC48-ADC, a HER2-targeting antibody-drug conjugate, or BCG, at West China Hospital of Sichuan University between 2019 and 2023. The primary study endpoint was the twelve-month recurrence-free survival (RFS) rate, with safety assessments as secondary endpoints. **Results:** A total of thirty patients diagnosed with HR-NMIBC displaying HER2 overexpression were included in the study. Following TURBT, eleven patients received adjuvant therapy with RC48-ADC, while nineteen received adjuvant therapy with BCG. The median follow-up duration for patients receiving RC48-ADC and BCG adjuvant therapy was 7.3 and 16.43 months, respectively. Among patients treated with RC48-ADC, the twelve-month RFS rate was 100%, with one out of the 11 patients experiencing relapse after 14.2 months of RC48-ADC adjuvant therapy. In the BCG-treated group, the twelve-month RFS rate was 57.6%. However, Kaplan-Meier analysis revealed no statistically significant difference between these two groups (P=0.22). In the RC48-treated group, the most commonly reported treatment-related adverse events (TRAEs) included alopecia (45.5%), arthralgia (18.2%), and nausea (18.2%). A total of 27.7% of patients experienced grade 3 TRAEs, including alopecia, rash, and hypoesthesia, with no observations of grade 4 or grade 5 TRAEs. **Conclusions:** RC48-ADC has demonstrated promising efficacy with a manageable safety profile as an adjuvant therapy in patients with HR-NMIBC. RC48 may be an alternative adjuvant therapy for BCG in terms of the 12-month recurrence-free survival rate. Research Sponsor: None.

Neoadjuvant nivolumab (N) + ipilimumab (I) in cisplatin-ineligible patients with upper tract urothelial cancer (UTUC): Updated results.

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Background: Perioperative platinum-based chemotherapy for UTUC improves pathologic responses and disease-free survival (DFS). We report the updated results from our on-going phase II neoadjuvant trial of N+I for cisplatin-ineligible patients (pts) with UTUC (NCT03520491). **Methods:** Cisplatin-ineligible pts with histologically confirmed high-grade UTUC and/or radiographically invasive UTUC with positive selective urine cytology were eligible. Pts were treated with I 3mg/kg + N 1mg/kg (weeks 0, 6), and "N" 3mg/kg (week 3) prior to radical nephroureterectomy (NU). The primary endpoint (EP) was pathologic complete response (pCR, ypT0pN0) and secondary EPs included <ypT2pN0 rate, DFS, and toxicity. Next generation sequencing of pre-treatment tumors was correlated with pathologic response. **Results:** Seventeen pts (76% male) were enrolled between 2/2021-6/2023 with median age 73 (range 59-85). Primary sites included ureter in 10 pts, renal pelvis in 5 and both in 2. Median tumor diameter was 3.0 cm, (range: 1.5 - 4.2 cm), with 8 pts (47%) having hydronephrosis. To date, 11 pts (65%) have received all planned treatment, 6 pts had N+/-I stopped early due to treatment-related toxicities, 2 pts are pending NU, 13 pts have undergone NU, 1 declined surgery, and another progressed on N+I. A pCR was seen in 4/15 pts (27%) and <ypT2pN0 in 9/15 (60%). Median time from last treatment to NU was 1.6 months (range 0.5-4.9). Three pts developed metastatic recurrence at 3.9, 10.3 and 15.6 months after treatment initiation. CTCAE grade ≥3 treatment-related adverse events occurred in 5 pts (29%). Four pts died during follow up: two of metastatic disease, one of complications related to a bowel leak (7.2 months after N+I initiation and 4.7 months after NU), and one from complications of a fall unrelated to disease or treatment (9.2 months after N+I initiation and 4.7 months after NU). Median tumor mutational burden (TMB) in 9 pts with pre-treatment sequencing was 13.2 mutations/mb (range 4.1-106.3), with 4/5 pts with TMB>10 <ypT2pN0 at NU. Pathogenic germline variants in mismatch repair genes were confirmed in 4 pts (MSH2 in 3, MLH1 in 1) and MSI-high tumors without germline alterations in 2 pts, with 5 of 6 completing NU (1 pending surgery); all 5 achieved pCR (n=3) or ypTaN0 (n=2) and remain alive and disease-free at last follow-up (6, 13.4, 17, 17.9 and 31 months). **Conclusions:** Updated findings from an on-going phase II trial of cisplatin-ineligible pts with UTUC receiving neoadjuvant N+I shows clinical activity in line with our initial results. All pts with pathogenic germline variants in mismatch repair genes or MSI-high tumors without germline alteration who underwent NU achieved <ypT2pN0 and remain free of disease. Clinical trial information: NCT03520491. Research Sponsor: None.

Real world experience of *FGFR* gene alterations and clinical outcomes in advanced/metastatic urothelial cancer in Japan: MONSTAR-SCREEN database study.

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Background: Gene alterations (GA) in fibroblast growth factor receptors (*FGFR*) may be oncogenic drivers in urothelial cancer (UC). However, the association between *FGFR* GA status and the prognosis with platinum-based chemotherapy has not been well investigated, especially in Asian patients. This study aims to elucidate the proportion and prognosis of *FGFR*2 or 3 (2/3) GA-positive advanced or metastatic UC (a/m UC). **Methods:** This study included patients registered during 2019 and 2022 in the "MONSTAR-SCREEN" database, where FoundationOneLiquid (F1L) was used for detecting 324 cancer-related genes, including *FGFR*. Analyzed *FGFR*2/3 GA variants included *FGFR*3 mutations (R248C, S249C, G370C, and Y373C) and *FGFR*2/3 fusions (FGFR2-BICC1, FGFR2-CASP7, FGFR3-TACC3, and FGFR3-BAIAP2L1). The positive ratio of *FGFR*2/3 GA and other gene alterations except *FGFR* was obtained at registration in eligible patients; besides, *FGFR*2/3 GA status was also evaluated after systemic treatment. Progression-free survival (PFS) in each treatment line was estimated, summarized by *FGFR*2/3 GA positive/negative. **Results:** Among the registered 2,224 cancer patients in this database, 138 eligible a/m UC patients were included (median age [SD] 72.0 [9.1] years for all; 95 males [68.8%]). The primary tumor site was the bladder in 70 patients (50.7%), renal pelvis in 50 patients (36.2%), and ureter in 18 patients (13.0%). *FGFR*2/3 GA was positive in 16 patients (11.6% [95% confidence interval: 6.8, 18.1]); the proportion of other typical gene alterations was 92.8%, 41.3%, 23.2%, and 23.2% in *TP53*, *TERT*, *ARID1A* and *BRCA2*, respectively. F1L was performed both before and after systemic treatment twice or more in 55 patients (39.9%). The *FGFR* concordance was analyzed in 55 patients available for both before and after treatment F1L results. Among them, 3 of the 6 *FGFR*2/3 GA-positive patients (50.0%) remained positive, and 1 of the 49 *FGFR*2/3 GA-negative patients (2.0%) before systemic treatment turned positive after treatment. The median PFS after first-line treatment was 6.8 months in *FGFR* GA-positive and 6.4 months in the negative patients. The estimated survival rate after first-line treatment was also similar between *FGFR* GA-positive and -negative patients at 12 months (68.8% vs. 81.0%). **Conclusions:** The results showed a similar trend to previous studies, where *FGFR* GA was reported in approximately 20% of metastatic UC patients. No difference was found in the PFS and the estimated survival rate by *FGFR*2/3 GA-positive or -negative patients. Our data showed that treatment pressure did not alter the *FGFR* status commonly. Research Sponsor: Janssen Pharmaceutical K.K.

AIM high: Epigenetic modulation and immune stimulation in bladder cancer.

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Background: Immune-checkpoint inhibitors (ICI) have emerged as valuable treatment options for patients with bladder cancer, particularly those who are ineligible for other therapies or have experienced disease progression on treatment. Response rates are only 20-30%, highlighting the need for biomarkers to predict treatment response and strategies to overcome resistance. Epigenetic modulators including the DNA methyltransferase (DNMT) inhibitor 5-azacitidine (AZA) and histone deacetylase inhibitors (HDACi) may represent co-targeting therapies in combination with ICI to enhance antitumor immunity. AZA has been demonstrated to increase the expression of a panel of immunomodulatory genes termed the "AZA Immune gene panel (AIM)" in breast, colorectal, and ovarian cancer cell lines. We hypothesized that bladder cancer with low AIM expression can be therapeutically converted by epigenetic modulation to "AIM-high" for future combination with ICI. **Methods:** Five human bladder cancer cell lines were selected: SCaBER, SW780, T24, RT4 and one developed at our institution (CoCaB1). The Cancer Cell Line Encyclopedia (CCLE) was used to screen the four included lines for intrinsic AIM expression, which were predicted to be AIM-high (n=1) and AIM-low (n=3). A cell viability assay was performed to screen for AZA and HDACi toxicity. Cells were treated with drug or vehicle for 72 hours and harvested at day 6, 14, and 21. RNA was extracted for RNA sequencing (RNA-seq) analyses. For analysis of AIM gene expression in clinical specimens, RNA-seq data was obtained from primary (n=6) and metastatic (n=83) bladder cancer specimens for 20 patients participating in the University of Washington Bladder Cancer Rapid Autopsy Program. **Results:** RNA-seq analyses of 5 cell lines demonstrated increased expression (>log 2-fold change, $p<0.05$) of a subset of AIM genes involved in inflammation, interferon, cytokine/chemokine signaling, and cancer testis antigens (CTA, a family of immunogenic proteins) with AZA treatment. Co-treatment with HDACi showed additional upregulation of AIM genes. Gene set enrichment analyses uncovered enrichment in T-cell pathway activation. In metastatic bladder cancer tissues, interferon, cytokine/chemokine, inflammation, and CTA AIM gene set categories were upregulated in a subset of patients. AIM gene enrichment displayed a patient-dependent pattern and was consistent across metastatic sites within a patient. **Conclusions:** Epigenetic priming therapy increases the expression of immunomodulatory and T-cell related genes in bladder cancer cell lines with low baseline AIM expression. Additional correlative studies in the rapid autopsy series will further determine clinical- and treatment-related factors contributing to intrinsic immune-related gene expression. Building on this paradigm, future *in vivo* and clinical studies could lead to novel combination therapies for patients with bladder cancer. Research Sponsor: Urology Care Foundation Research Scholar Award; Department of Defense Peer-Reviewed Cancer Idea Award; Seattle Tumor Translational Research (STTR) Program; Paul H. Lange Chair in Urologic Oncology.

649 Poster Session

Performance of a tumor-informed molecular residual disease (MRD) assay in resected bladder cancer with mixed or pure variant histology: Analysis of a real-world multicenter cohort.

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Background: Circulating tumor DNA (ctDNA)-based MRD assays can detect clinically occult disease with high sensitivity and specificity in patients with solid tumors. Previous trials that evaluated MRD testing in bladder cancer, such as ABACUS and IMVigor010, enrolled patients with a predominant urothelial carcinoma component. Given the known histological and molecular heterogeneity in urothelial carcinoma, we examined the prognostic value of a tumor-informed MRD assay in bladder cancer patients with mixed or pure variant histologies (M/VH). **Methods:** This retrospective study analyzed the results of post-cystectomy longitudinal ctDNA testing from a multi-institutional database of patients with urothelial carcinoma (n=205). A personalized, tumor-informed assay (Signatera, Natera, Inc.) was used for the detection and quantification of ctDNA. Patients with M/VH and at least 3 months of post-operative follow-up data on relevant demographic, clinical, pathologic, and NGS variables were eligible for inclusion. Time-dependent Cox regression analyses were performed for disease-free survival (DFS) based on ctDNA during the MRD window (<12 weeks from surgery, N=29) and surveillance window (>12 weeks post-surgery or post-AT, N=29). Multivariable regression was performed to adjust hazards for clinicopathologic factors predicting DFS. **Results:** Of the 205 patients, 46 (74% male, median age: 69 years) met the inclusion criteria for analysis. Whole exome sequencing of tumor tissue revealed that TP53 (45.7%), ARID1A (32.6%), and KDM6A (30.4%) were the top three genes with somatic mutations. Twenty-seven (59%) patients received neoadjuvant therapy, 37% of whom (10/27) also received adjuvant therapy. ctDNA-positivity during the MRD window and during surveillance was strongly associated with poor DFS (MRD window: HR=4.93, 95%CI: 1.77-20.77, p=0.03; surveillance: HR=28.3, 95% CI: 3.52-3660, p<0.001). None of the serially ctDNA-negative patients (N=25) recurred, whereas 58.9% (10/17) of patients who were ctDNA-positive anytime post-surgery recurred at a median follow-up of 9 months from the date of surgery, range: 3.1-36.4 months). When adjusted for all other risk factors, ctDNA-positivity anytime post-surgery was the only significant predictor of recurrence (HR=55.26, 95%CI: 5.3-7648, p<0.00001). **Conclusions:** Personalized, tumor-informed ctDNA testing can identify patients with mixed or variant histology bladder cancer who are at high risk of recurrence. Further studies are warranted to evaluate the potential benefit of ctDNA-guided adjuvant therapy in this patient population. Research Sponsor: None.

Genomic comparison of urothelial mucinous adenocarcinoma and colorectal mucinous adenocarcinoma biomarkers and therapeutic implications.

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Background: Urothelial mucinous adenocarcinoma (UC-MUC-AC), arising from the urothelium, is a rare condition (<2%), typically presenting at an advanced stage with an unfavorable prognosis. The lack of a standard treatment protocol adds complexity, requiring the extension of treatments from UC or organ-specific MUC-AC such as colorectal. Notably, UC-AC bears a histopathological resemblance to intestinal tumors, constituting the predominant subtype. Alternatively, treatment decisions based on gene expression similarities in lieu of histological similarities are an evolving concept in rare cancers. This is an unexplored area in UC-MUC-AC treatment, prompting our hypothesis that an all-encompassing genomic profile could reveal analogous biomarkers shared with CRC-MUC-AC. **Methods:** Three techniques: DNA sequencing, RNA sequencing (WTS), and immunohistochemistry (IHC) sequencing (protein) with varying measures for gene expression were analyzed at Caris Life Sciences in Phoenix, AZ. Histopathology was used to categorize five cancer site groups: (1) UC arising in the bladder, ureter, urethra, or renal pelvis with any transitional cell carcinoma (TCC)-non-MUC-nonAC [N156 samples], (2) UC nonTCC-nonMUC-AC [N83], (3) UC-MUC-AC [N16], (4) CRC-MUC-AC [N3100] and (5) CRC nonMUC-AC [N38205]. Our primary aim was to determine which group was closest to Group 3, our control. Our secondary aim was to determine if Group 2 was genetically closer to Group 1 or 5. Only genes with positive expression were included in the cluster analysis. ANOVA analysis was conducted to further explore the relationships between the groups. A log transformation was performed to achieve normality. To further investigate pairwise comparisons, a post hoc Dunnett test was employed. **Results:** In our first analysis, Group 3 UC-MUC-AC gene expression ratio was predominately associated with UC Groups 1 & 2 (24 of 33), and farther to CRC Groups 4 & 5 (9/33) (all p-values >0.05). In the second analysis, the ANOVA overall model comparing gene expression between the histological groups 1, 2 & 5 was statistically significant (p=0.0018). The Dunnett test revealed a farther difference between Group 2, UC nonTCC-nonMUC adenocarcinoma, and 5, CRC non-MUC-AC (p-value =0.001), but closest between Group 2 and 1, UC-TCC-nonMUC-nonAC (p =0.100). **Conclusions:** Our findings indicate that next-generation sequencing technology has the potential to aid in treatment decisions based on the site of origin, such as UC-AC, rather than relying on traditional histopathological descriptive approaches for extrapolating evidence from treatment protocols used for other cancer origins like CRC. Future research on artificial intelligence could aid physicians with more informed treatment decisions by providing additional insight into how closely tumors match cancer types' genomic and transcriptomic signatures. Research Sponsor: None.

Impact of squamous histology on outcomes with enfortumab vedotin in patients with advanced urothelial carcinoma: Analysis of the UNITE study.

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Background: Squamous histology (SH) is the most common variant of Urothelial Carcinoma (UC) and is associated with lower response rates to chemotherapy. The impact of SH on outcomes with enfortumab vedotin (EV) is less defined. We hypothesized that increased SH component would correlate with inferior outcomes with EV treatment. **Methods:** UNITE is a multi-institutional retrospective study in pts advanced UC (aUC) treated with targeted agents. In this analysis, we compared EV monotherapy outcomes in pts with pure UC (pUC) and pts with urothelial predominant histology (UCP) [<50% SH], SH-predominant [50-99% SH] and pure SH (pSH) [100% SH] respectively. We also compared pSH to UCP and SHP. Observed Response Rate (ORR) was compared in evaluable pts with scans after ≥1 cycle of EV using Chi-squared test. Progression-free survival (PFS) and overall survival (OS) from EV start were assessed and compared using the KM method and Cox proportional hazard test. **Results:** This analysis included 460 pts from 17 US sites treated with EV monotherapy. 366 pts had pUC and 94 pts had SH component (including pSH). In the overall cohort, median age was 70, 73% men, 88% Caucasian, 73% ECOG PS 0-1, 67% lower tract tumor, 30% liver mets, 38% bone mets, 65% had ≥ 2 prior therapy lines. There were no significant differences in baseline clinical characteristics between pts with pUC vs SH component except for higher incidence of liver mets in pts with pUC (32% vs 20%; p = 0.02). Among all 460 pts, median follow up was 20.7 mos from EV start, ORR was 51%, mPFS and mOS were 5.8 mos (95% CI: 5.3-6.4) and 12.7 mos (95% CI: 11.5-14.3). Among 94 pts with SH component, 70 were UCP, 17 SHP and 7 pSH. Inferior outcomes were noted in pts with pSH relative to pts with pUC and pts with UCP (Table). No differences in outcomes were seen across other cross-group comparisons. **Conclusions:** These hypothesis-generating findings suggest that SH component may impact outcomes with EV treatment in pts with aUC. A subset of pts with SH-predominant histology can have robust responses and outcomes with EV treatment, but larger studies and further biomarker data are needed to determine pts most likely to benefit. Patients with pSH are shown to have worse outcomes with EV, but further studies with a larger sample size are needed to validate our findings and define the role of EV for this rare and biologically distinct entity. Research Sponsor: None.

	Pure Urothelial[a] (pUC, n=366)	Urothelial Predominant[b] (UCP, n=70)	SH-predominant (SHP, n=17)	Pure Squamous[c] (pSH, n = 7)
ORR[1]	52% (167/319)	55% (31/56)	33% (5/15)	0% (0/5)
mPFS[2], mos (95% CI)	5.8 (5.5 – 6.9)	5.3 (3.9 – 12.0)	3.7 (1.6 – NR)	3.5 (1.6 – NR)
mOS[3], mos (95% CI)	13.1 (11.5 – 15.2)	12.7 (8.3 – 18.4)	10.6 (4.4 – NR)	4.1 (2.3- NR)

1. a vs c, p =0.02; b vs c, p =0.02; 2. c vs a – HR: 1.95 (95% CI: 0.92 – 4.14), p =0.08, c vs b – HR: 2.10 (95% CI: 0.95 – 4.65), p =0.07; 3. c vs a – HR: 2.92 (95% CI: 1.29 – 6.61), p <0.01, c vs b – HR: 2.7 (95% CI: 1.13 – 6.43), p =0.03.

Outcomes with enfortumab vedotin in patients with advanced urothelial carcinoma and histology variants: Analysis of the UNITE study.

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Background: Enfortumab vedotin (EV) is approved for patients (pts) with advanced urothelial carcinoma (aUC) but outcomes in pts with histology variants (HV) have not been well described. We hypothesized that presence of HV would impact EV treatment outcomes. **Methods:** UNITE is a multi-site retrospective study of pts with aUC treated with targeted agents, including 650 pts treated with EV regimens. We compared outcomes to EV monotherapy in pts with pure UC (pUC) relative to pts with any HV and with specific HVs. In pts with scans after >1 cycle of EV, observed response rate (ORR) was assessed using χ^2 test and logistic regression. Median progression-free survival (PFS) and overall survival (OS) from EV start were measured using the Kaplan Meier method and Cox proportional hazard test. **Results:** A total of 566 pts (366 with pUC; 200 with HV) from 17 US sites were treated with EV monotherapy. Median age was 70 years, 71% men, 87% Caucasian, 74% with ECOG PS 0/1 and 28% with liver mets. Median follow up was 21 mos from EV start, ORR was 49%, mPFS and mOS were 5.8 mos (95% CI: 5.29-6.67) and 12.2 mos (95% CI: 11.5 – 13.8), respectively. Pts with pUC had more visceral mets (69% vs 60%, p = 0.04) and liver mets (32% vs 21%, p =0.003) than pts with HV. No significant difference in outcomes were seen between pUC and pts with HV component (1-100%). Pts with predominant HV (50-99%; N=35), had numerically lower ORR relative to pUC pts (36% vs 52% OR 0.31, p <0.09), but no difference in mPFS or mOS. Pts with pure HV (pHV) (100%: N=14) had inferior outcomes relative to pts with pUC (ORR 0% vs 52%, p<0.001; mOS HR: 2.96 (95% CI: 1.60 – 5.46), p <0.001; mPFS HR: 1.9 (95% CI: 1.06 – 3.39), p=0.03). ORRs for specific HV are listed in the table. No significant difference in treatment outcomes were seen in pts with pUC vs any specific HV, except for NE HV which had inferior ORR (0% vs 52%; p=0.003). **Conclusions:** Responses to EV are noted in some aUC pts with HV, except for NE (any component) and pHV. Certain HV notable for poor outcomes, such as sarcomatoid and plasmacytoid, demonstrated responses to EV. These hypothesis-generating findings require further validation in studies with adequate sample size for specific HV, and in particular pHV. Evaluation of biomarkers, including Nectin4 expression, in HV is paramount. Research Sponsor: None.

Variant	ORR	UC Predominant (<50% HV)	ORR	HV Predominant (50-99% HV)	ORR	pHV (100% HV)	ORR
Squamous (n = 94)	47% (36/76)	70	55% (31/56)	17	33% (5/15)	7	0% (0/5)
Micropapillary (n = 41)	35% (12/34)	35	38% (11/29)	6	20% (1/5)	0	-
Plasmacytoid (n=23)	53% (9/17)	18	64% (9/14)	2	Not Evaluable	3	0% (0/3)
Sarcomatoid (n=21)	47% (8/17)	15	38% (5/13)	4	100% (3/3)	2	0% (0/1)
Adenocarcinoma/Glandular (n=9)	56% (5/9)	8	63% (5/8)	1	0% (0/1)	0	-
NE/Small Cell (n = 9)	0% (0/8)	3	0% (0/3)	4	0% (0/3)	2	0% (0/2)
Nested (n=2)	50% (1/2)	1	0% (0/1)	1	100% (1/1)	0	-
Lipid Cell Variant (n=1)	100% (1/1)	1	100% (1/1)	0	-	0	-
Any VH	44% (72/164)	151	50% (62/125)	35	36% (10/28)	14	0% (0/11)

Comprehensive genomic profiling (CGP) of clinical T2-4N0M0 muscle-invasive bladder cancer (MIBC) treated with neoadjuvant pembrolizumab or cisplatin-based chemotherapy before radical cystectomy (RC).

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Background: The identification of tumor biomarkers associated with pathological complete response (CR: ypT0N0) to neoadjuvant therapies is a primary goal of the ongoing clinical research in MIBC. Furthermore, evaluating the shifting spectrum of genomic alterations (GA) in matched pre-post therapy samples could orient novel therapeutic sequences. **Methods:** We retrospectively evaluated the clinical and genomic findings of patients (pts) with cT2-4N0M0 MIBC who received neoadjuvant pembrolizumab in the PURE-01 study, or standard cisplatin-based neoadjuvant chemotherapy (NACT), preceding RC at our center. We focused the analyses on the DNA GA via CGP assays, performed on tumor samples, to identify GA in 324 cancer-associated genes and genomic signatures, including TMB, using a hybrid capture-based comprehensive genomic profiling assay. TMB was categorized as low (<10 mutations [mut]/Mb), high (10-19), or very high (≥20). Germline status of GA was predicted using a validated somatic-germline computational method. Genomic signatures were analyzed via the principal Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways distribution according to the pathological response. The primary endpoint was to compare differences between ypT0N0 responders and nonresponders (NR: ypT≥2 and/or ypN1-3). All *p*-values were two-sided, and multiple hypothesis testing correction was performed using the Benjamini–Hochberg procedure to calculate the false discovery rate (FDR). **Results:** We identified TURBT samples from 129 pts included in PURE-01 and 27 patients treated with NAC, from 2017 to 2022. Mean GA/tumor of CR from PURE-01 was 28.8 vs 17.3 from NAC. No germline GA were found. In PURE-01, higher mean GA/tumor and higher mean TMB were the only GA associated with CR vs NR ($p<0.001$), whereas no differences were found at single gene and gene pathways level. In NAC cohort, no GA nor signatures were found to be significantly associated with CR. Despite the mean TMB of CR pts were similar between PURE-01 and NAC cohorts (16.4 vs 19.6 mut/Mb), mean TMB of NR in PURE-01 cohort was lower than that of NR from NAC cohort (9.3 vs 18.6 mut/Mb). In PURE-01 we analyzed 37 matched TURBT-RC samples: there were no significant differences in GA or pathways, with a nonsignificant decrease in mean TMB values in RC vs TURBT samples (6.73 vs 8.86 mut/Mb, p=0.16). **Conclusions:** In our study, no genomic biomarkers linked to NAC activity emerged at the CGP. Conversely, in PURE-01 TMB confirmed to be to most reliable DNA biomarker to separate CR vs NR. Interestingly, TMB values could also help predicting the lack of benefit from neoadjuvant pembrolizumab use, confirming the reliability of the 10 mut/Mb cutoff to allow the exclusion of predicted nonresponders from neoadjuvant pembrolizumab trials. Research Sponsor: None.

Role of tumor mutational burden (TMB) and microsatellite instability (MSI) in patients (pts) with advanced urothelial carcinoma (aUC) treated with immune checkpoint inhibitor (ICI).

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Background: MSI and TMB correlate with ICI efficacy. We assessed the association between TMB and MSI with outcomes in pts with aUC treated with anti-PD1/L1 in a 'real-world' cohort. We hypothesize that pts with high TMB and MSI-high (H) have better outcomes with ICI. **Methods:** In this retrospective study we included pts from 13 sites treated with ICI for aUC. We calculated overall response rate (ORR), median overall and progression-free survival (mOS, mPFS) using KM method from ICI start. TMB and MSI were assessed by NGS. TMB was analyzed as dichotomous (≥10 vs <10 mut/Mb) and continuous variable. The analysis was stratified by therapy line (1L/upfront, 2+L). Multivariable models were adjusted by Khaki factors for 1L/upfront and Bellmunt factors for 2+L. We separately analyzed pts on maintenance avelumab (mAV). MSI is reported with descriptive statistics only. **Results:** 342 pts were treated with ICI 1L/upfront or 2+L (69% pure UC, median age at ICI start 69, 77% men, 90% White, 16% upper tract primary, 12% liver metastases [mets], 78% ECOG PS 0-1). Median f/u from ICI start was 34 months (mo). ORR was 36% (95%CI 26-46%) in pts with TMB≥10 vs 30% (95%CI 23-36%) with TMB<10 (OR=1.4 [95%CI 0.8-2.5] p=0.3). ORR was 75% (6/8) in pts with MSI-H and 30% (60/200) with MSI stable (MSI-S). mPFS was similar between TMB≥10 and <10 groups (6 vs 4 mo; HR=0.88 [95%CI 0.61-1.26] p=0.48) and between MSI-H and MSI-S (5 mo). mOS was numerically longer (not significant) in pts with TMB≥10 vs TMB<10: 25 vs 21 mo; (HR=0.7 [95%CI 0.50-1.09] p=0.12) and with MSI-H and MSI-S (NR and 20 mo). A significant association was found between TMB (continuous variable) and OS (HR=0.97 [95%CI 0.95-0.99] p=0.01). TMB analyses by therapy line are shown in Table. In the 1L/upfront setting (N=144), ORR 71% (5/7) vs 33% (45/135), mPFS 5 and 4 mo, mOS NR and 22 mo for MSI-H and MSI-S, respectively. Pts on mAV (n=77) were 77% men, 92% White, 16% upper primary, 13% liver mets, 84% ECOG PS 0-1 with median f/u 15 mo from avelumab start; mOS was NR for MSI-H and 24 mo for MSI-S; mPFS was 4 mo for both groups. Of 3 pts on mAV with MSI-H: 1 CR, 2 SD; of 58 pts with MSI-S: 4CR, 4PR, 24 SD, 21 PD, 5 unknown. **Conclusions:** MSI-H had numerically higher ORR and higher TMB was associated with longer OS with ICI, but further validation is needed. Limitations: retrospective design, small sample size for MSI-H cases, lack of randomization and central scan review, selection/confounding. Research Sponsor: None.

	N	ORR N (%)	OR (95%CI)	N	mPFS mo (95%CI)	HR (95%CI)	N	mOS mo (95%CI)	HR (95%CI)
1L									
TMB<10	123	44 (36%)	Ref	88	4	Ref	123	25 (17-34)	Ref
TMB≥10	64	23 (36%)	0.9 (0.4-1.9)	39	7	0.7 (0.4-1.0)	65	35 (12-57)	0.7 (0.4-1.2)
2+L									
TMB<10	59	11 (19%)	Ref	49	4	Ref	60	16 (12-20)	Ref
TMB≥10	23	4 (17%)	0.6 (0.1-2.5)	17	4	1.5 (0.8-2.8)	23	20 (12-28)	1.3 (0.7-2.5)
mAV									
TMB<10	40	4 CR, 4 PR, 14 SD, 17 PD, 1 unknown		27	3	Ref	39	24.2	Ref
TMB≥10	28	4 CR, 1 PR, 13 SD, 6 PD, 4 unknown		19	4	0.7 (0.3-1.5)	27	NR	0.5 (0.1-2.7)

Mutational signature and prognosis in adenocarcinoma of bladder.

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Background: Adenocarcinoma of bladder is a rare urinary bladder carcinoma with limited therapy options due to lack of molecular characterization. Here we aim to reveal mutational and transcriptomic landscapes of adenocarcinoma of bladder and their relationship with prognosis. **Methods:** Between February 2015 and June 2021, a total of 23 patients with adenocarcinoma of bladder were included. These included 16 patients with primary bladder adenocarcinomas and 7 patients with urachal adenocarcinoma. Whole exome sequencing, whole genome sequencing, bulk RNA-Seq and single-cell RNA-Seq were conducted for the specimens. Correlation analysis, survival analysis and *t* tests were also performed. **Results:** Prevalent T>A substitutions were observed among somatic mutations, and major tri-nucleotide contexts included 5′-CTC-3′and 5′-CTG-3′. This pattern was mainly contributed by COSMIC Signature 22 related to chemical carcinogen exposure (probably aristolochic acid), which has not been reported in bladder adenocarcinoma. Moreover, genes with copy number changes also enriched KEGG term "chemical carcinogenesis". Transcriptomic analysis implied high immune infiltration and luminal-like feature in majority of samples. Interestingly, a small fraction of samples with APOBEC-derived mutational signature exhibited higher risk of disease progression compared with samples with only chemical carcinogen-related signature, confirming molecular and prognosis heterogeneity in bladder adenocarcinoma. **Conclusions:** This study presents mutational and transcriptomic landscapes of bladder adenocarcinoma, and chemical carcinogen-related mutational signature indicates good prognosis in adenocarcinoma of bladder. Research Sponsor: None.

Association of ARID1A deficiency with invasive transformation in metastatic bladder cancer.

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Background: ARID1A is an essential component of the BAF complex, a large SWI/SNF chromatin-remodeling complex which is implicated in bladder cancer (BC) pathogenesis. While ARID1A mutations are more highly represented in metastatic rather than localized tumors, the biological consequences of ARID1A loss in BC remain to be elucidated. We hypothesize that ARID1A deficiency primes an invasive transformation in BC, thus increasing the likelihood of disease progression and metastases. We used CRISPR/Cas9-mediated gene editing to knockout (KO) the ARID1A gene in several BC cell lines, thus providing a platform for cellular function assays. We show that ARIDA1 loss potentiates an invasive phenotype in these cell lines, giving evidence for its transformative role in the development of higher stage and metastatic BC. **Methods:** A CRISPR-Cas9 KO was performed with three cell lines with wild-type (WT) ARID1A (T24, SW1710, and 5637). This was accomplished by developing sgRNAs against ARID1A with a GFP marker and carrying out single-cell fluorescence-activated cell sorting (FACS) following nucleofection to identify ARID1A-deficient clones. Western blot analysis was performed on the resulting clones to confirm complete loss of ARID1A. Baseline proliferation studies were performed on the KO and WT cell lines. Finally, invasion studies were performed on the KO and WT cells with a scratch assay. **Results:** CRISPR-Cas9 directed KO of ARID1A yielded ARID1A-deficient clones for SW1710, T24, and 5637. The proliferation rates for each cell line were analyzed and compared which showed no significant differences. A scratch assay was performed with the cell lines in triplicate, with each ARID1A-deficient cell line showing a trend towards more rapid wound closure than its matched WT cell line (WT=31.5% vs. KO=53.5% for SW1710, p=0.15; WT=17.2% vs. KO=52.0% for T24, p=0.07; WT=10.4% vs. KO=13.9% for 5637, p=0.59). **Conclusions:** To explore the increased frequency of ARID1A alterations in metastatic BC compared to non-invasive tumors, we developed a model of ARID1A-deficient BC using CRISPR-Cas9. We compared the relative invasiveness of the lines using a scratch assay. All lines trended towards a more invasive phenotype following ARID1A KO, which was especially pronounced in T24. Taken together, these data suggest that ARID1A deficiency in BC may prime tumors for a more invasive phenotype, which may help to explain the higher frequency of ARID1A alterations in higher stage and metastatic samples. Research Sponsor: None.

Genomic profiling of bladder cancer in waterpipe and cigarette smokers: Implications for carcinogenicity and genetic landscape.

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Background: While cigarette smoking is a well-established risk factor for bladder cancer (BC), limited research has explored the contribution of waterpipe smoking (WPS) to BC. WPS is gaining popularity among Middle Eastern youth, often perceived as a safer alternative to cigarettes. Alarmingly, Lebanese males had an age-standardized incidence rate of 54.0 per 100,000 in 2019, the highest in the Arab World and five times the global average, prompting a critical investigation into potential risk factors. Mounting evidence suggests that WPS exposes users to toxicants and carcinogens that can induce chromosomal damage contributing to cancer. This study aims to assess the genomic and mutational profiles of BC in waterpipe smokers compared to cigarette smokers. **Methods:** This cross-sectional study enrolled adults with urothelial carcinoma (UC) who exclusively smoked waterpipe at the American University of Beirut Medical Center (AUBMC) between April 2017 and September 2019. Next-generation sequencing by MSK-IMPACT characterized mutational profiles, tumor mutation burden, and microsatellite instability (MSI) status in tumor-normal pairs. For comparison, a cohort from Memorial Sloan Kettering Cancer Center (MSKCC), comprising previously profiled BC tumors from cigarette smokers, was used. **Results:** A total of 14 exclusively WPS-BC patients were enrolled, with 12 males (85.7%) and a median age at diagnosis of 62.9 years (range: 30.7 to 78.9). Among these patients, 9 (64.3%) had non-muscle invasive BC, with 8 (57.2%) classified as high-grade UC. MSK-IMPACT sequencing successfully analyzed 13 WPS samples, revealing genomic patterns similar to the cigarette smoking cohort. Common genetic alterations in the WPS cohort included mutations in TERT promoter (62%), TP53 and FGFR3 (46% each), and PIK3CA (38%). Mutations in chromatin modifiers were less prevalent, with the highest frequencies observed in KDM6A (31%) and KMT2C (15%). The tumor mutation burden was higher in the WPS group (22 per MB) compared to the cigarette smoking cohort (9 per MB), with no definite evidence of MSI. PD-L1 expression was generally low, with only 2 samples exhibiting combined positivity scores (CPS) of 15 and 10, primarily associated with immune cells PD-L1 expression. Only one tumor demonstrated 3% PD-L1 expression on tumor cells, while 7 tumors displayed no expression on either tumor or immune cells (CPS of 0). **Conclusions:** This study underscores the genomic similarities between BC in waterpipe and cigarette smokers. The preliminary findings, limited by sample size, highlight the need for further investigations to elucidate the potential role of WPS in BC development. Future efforts will focus on cohort expansion to validate initial observations, raising awareness of health risks associated with WPS, and emphasizing the importance of continued research to inform preventive strategies.
Research Sponsor: Bristol Myers Squibb.

A study of blood myeloid-derived suppressor cells for predicting pembrolizumab efficacy in patients with metastatic urothelial carcinoma.

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Background: Immune checkpoint inhibitors (ICIs) are crucial for treating metastatic urothelial carcinoma (mUC) patients, yet current prognostic biomarkers fail to predict ICI efficacy. Previous preclinical models have suggested myeloid-derived suppressor cells (MDSCs) as a potential therapeutic target in bladder cancer. This study aims to evaluate the predictive value of blood MDSCs in mUC patients undergoing pembrolizumab treatment. **Methods:** Ninety-eight mUC patients who progressed with platinum-based chemotherapy at Osaka Metropolitan University received pembrolizumab. Among them, 30 patients were assessed for blood MDSCs. Peripheral blood samples were collected from healthy individuals (n = 6) and mUC patients (n = 30) before pembrolizumab initiation. The mononuclear cell layer was isolated using density gradient centrifugation for MDSC analysis through flow cytometry. Monocytic and polymorphonuclear MDSCs were defined as CD11b+ HLADR − CD33 high CD14 + CD15 − and CD11b+ HLADR − CD33 low CD14 − CD15 +, respectively. The neutrophil-lymphocyte ratio (NLR) in blood served as a control. Treatment response was assessed via CT images using RECICT v1.1. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan-Meier method, with log-rank test for between-group comparison. **Results:** First, blood MDSCs were significantly elevated in mUC patients compared to healthy controls (p = 0.0024, Mann Whitney test). Secondly, patients with $MDSC^{low}$ ($\leq$ median, n = 15) had significantly longer PFS than those with $MDSC^{high}$ ($>$ median, n = 15) (17.6 vs. 1.9 months, p = 0.0126). However, no significant difference was observed in OS. In contrast, when the NLR cutoff was set at 3.5, no significant association was found for PFS and OS. **Conclusions:** Blood MDSCs show promise as a predictive marker for pembrolizumab therapy efficacy. Research Sponsor: None.

Predictive roles of NETs and IgG in neoadjuvant chemotherapy for muscle-invasive bladder cancer.

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Background: Cisplatin-based chemotherapy is the recommended therapy for muscle-invasive bladder cancer (MIBC), in the neoadjuvant setting. However, the efficacy of MIBC for chemotherapy is only about 40%. Therefore, predictors of therapy response are urgently needed. Neutrophils form neutrophil extracellular traps (NETs), a network structure, and growing evidence indicated that it could be a prognostic and predictive marker in cancer. Besides, NETs and IgG could reflect the immune response, even may induce immune tolerance. In MIBC, the predictive role of NETs or IgG in chemotherapy resistance is unclear. **Methods:** This study included 54 patients with MIBC undergoing neoadjuvant chemotherapy. Immunohistochemical staining with NETs was performed on tumor primary lesions before chemotherapy, and the staining intensity was scored. Serum IgG levels in the pre-treatment baseline and 1 month after chemotherapy were also measured for these patients. **Results:** Citrullinated histone H3 (H3Cit) as a hallmark of NETs, was an independent predictor of chemotherapy resistance as determined by the multivariate logistic regression analyses [OR=5.94, 95% CI 1.20–45.50, P=0.045]. Additionally, in patients with favorable chemotherapy response, serum IgG levels significantly decreased after 1 month of treatment (P=0.0018), while in those with poor response, there was no significant change. **Conclusions:** The baseline levels of NETs and the change of IgG after 1-month treatment demonstrated predictive capabilities during neoadjuvant chemotherapy, possibly reflecting the immune status. MIBC patients with high NETs and IgG levels were resistant to neoadjuvant chemotherapy, providing new insights into the treatment of MIBC. However, these results require further validation through larger sample studies. Further validation of our findings could provide a theoretical basis regarding NETs inhibitors or IgG antibodies combined with chemotherapy strategy. Research Sponsor: Beijing Municipal Natural Science Foundation.

Association of perioperative acute kidney injury with oncological outcomes in patients who undergo radical cystectomy: A multicenter retrospective study.

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Background: Acute kidney injury (AKI) is a frequent complication in patients with muscle-invasive bladder cancer (MIBC) who undergo radical cystectomy (RC). Previous studies have reported that AKI during cancer treatment was associated with poor oncological outcomes in several malignancies. Moreover, we previously have reported the negative impact of neo-adjuvant chemotherapy-induced AKI on oncological outcomes in patients with MIBC. However, the impact of perioperative AKI on oncological outcomes in patients who undergo RC remains unclear. **Methods:** This multi-institutional retrospective study included 798 patients with MIBC who underwent RC. AKI was defined according to the KDIGO criteria. Stage 1 AKI was diagnosed with an increase in serum creatinine by just 0.3 mg/dL. Patients were divided into two groups: patients who developed AKI after RC (AKI group) and patients who did not (non-AKI group). Multivariable Cox-proportional hazards regression analyses were performed to evaluate the impact of perioperative AKI on recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS). **Results:** The median age and follow-up period were 70 years and 64 months, respectively. Of the 798 patients, 408 (51%) developed AKI after RC. Approximately 73% AKI were stage 1 AKI. RFS, CSS, and OS in the AKI group were significantly shorter than those in the non-AKI group (P = 0.003, P = 0.035, and $P < 0.001$, respectively). After adjustment for confounding variables, AKI was significantly associated with shorter RFS (hazard ratio [HR] 1.357, P = 0.019), CSS (HR 1.345, P = 0.042), and OS (HR 1.344, P = 0.009). **Conclusions:** Perioperative AKI was associated with poor oncological outcomes in patients with MIBC who underwent RC. Research Sponsor: None.

Multivariable analyses.

	Factor	*P* value	Hazard ratio	95% CI
RFS*	AKI	0.019	1.357	1.052–1.749
CSS*	AKI	0.042	1.345	1.011–1.791
OS*	AKI	0.009	1.344	1.078–1.677

*Adjusted for age, performance status, neoadjuvant chemotherapy, tumor grade, variant histology, pathological T stage, lymphovascular invasion, pathological lymph node involvement, positive surgical margin, and neobladder reconstruction. CI, confidence interval.

Single-center analysis on a real-world cohort of patients with metastatic urothelial carcinoma studied by NGS: Molecular landscape and efficacy of targeted therapies.

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Background: the median overall survival (OS) in metastatic urothelial carcinoma (mUC) treated with multiagent therapy is approximately 13 months (mo). Around 69% of these tumors harbor potential therapeutic targets. Real-world evidence on using Next Generation Sequencing (NGS) in mUC management is limited. **Methods:** we conducted a single-center analysis on a real-world cohort of patients (pts) with mUC. The study population included pts aged >18 years with diagnosis of mUC studied by NGS at the moment of starting immunotherapy (enrollment period: 09/04/2019 – 03/25/2022). Median OS and median progression-free survival (PFS) were determined using Kaplan-Meier curves. **Results:** we included 43 pts. Median age at mUC diagnosis was 67 years; 38 (88.4%) pts were men; 38 (88.4%) pts were ECOG 0-1 at mUC diagnosis; one or more adverse prognostic factors (Bellmunt Risk Score) were identified in 33 (76.7%) pts; primary tumor site was lower tract in 36 (83.7%) pts. All pts were treated with platinum-based combinations (neoadyuvant, adyuvant or first line) and immunotherapy. Pathogenic alterations were found in 25 (58.1%) pts. In the group of 25 pts with pathogenic alterations, 17 pts progressed to immunotherapy and 7 pts of them received targeted therapies; 10 pts could not receive targeted therapies due to poor prognosis. In the group of 18 pts without pathogenic alterations, 11 pts progressed to immunotherapy and 8 pts of them received other chemotherapy options; 3 pts could not receive other chemotherapy options due to poor prognosis. The median OS (time since mUC diagnosis) among 25 pts with pathogenic alterations was 30.2 (CI 95%: 18.9-41.5) mo compared to 22.9 (CI 95%: 12-33.9) mo among 18 pts without pathogenic alterations, (p = 0.557). Focusing on the subgroup of 7 pts treated with targeted therapies (Table), we found an objective response rate (ORR) of 42.9%; the median PFS was 7.3 (CI 95%: 6.7-7.9) mo and the median OS (time since beginning targeted therapies) was 10.9 (CI 95%: 2.4-19.5) mo. **Conclusions:** We recommend that all pts with mUC undergo NGS at the time of diagnosis, given the high percent (58.1%) of pathogenic alterations in our real-world cohort and the efficacy in terms of ORR, PFS and OS in pts treated with targeted therapies.
Research Sponsor: None.

Pathogenic Alteration	Targeted Therapy	Line of Therapy (L)	Best Response	PFS (mo)	OS (mo)
ERBB2 p.(S310Y) c.929C>A	Neratinib	3L	Stable disease	7.3	10.9
FGFR3 p.(S249C) c.746C>G	Erdafitinib	5L	Partial response	7.1	7.6
ERBB2 mutation	Neratinib	4L	Progression	1.7	2.1
ERBB2 p.(S310F) c.929C>T	Neratinib	2L	Partial response	11.6	11.8
FGFR3 p.(R248C) c.742C>T	Erdafitinib	3L	Stable disease	8.1	13.1
ERBB2 amplification	Trastuzumab pertuzumab	2L	Stable disease	2.5	3.1
ERBB2 mutation	Trastuzumab deruxtecan	3L	Partial response	9.2	15.2

The role of androgen response pathway in association with tumor biology and response to neoadjuvant immune-checkpoint inhibitors (ICI) in muscle-invasive urothelial bladder carcinoma (MIBC).

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Background: Emerging findings from ICI trials are suggestive of differential outcomes in females compared with males. Sex-specific differences in tumor biology, microbiome, and outcomes in MIBC are well-established. Conversely, limited data are available regarding the role of the androgen response pathway in explaining subtype differences between males and females and, most importantly, response to ICI. **Methods:** We retrospectively evaluated the biomarker findings of the transurethral resection of the bladder tumors (TURBT) and baseline clinical characteristics of patients (pts) with cT2-4N0M0 MIBC who received neoadjuvant pembrolizumab and radical cystectomy (RC) in the PURE-01 study. Transcriptome-wide expression profiling was performed on 102 TURBT samples. We focused on androgen receptor (AR) gene expression and the hallmark androgen response pathway expression quantifying 117 different genes related to the androgen response pathway as previously reported (PMID: 26771021). Pt and tumor characteristics were compared between subgroups using $\chi 2$ tests and two-sided Wilcoxon rank-sum tests. Kaplan-Meier curves and log rank tests evaluated gene expression and signature scores in association with the event-free survival (EFS), calculated from start of pembrolizumab treatment. Signature scores were analyzed as continuous values and were split by median and quartile values. **Results:** Pts received pembrolizumab and RC from 2017 to 2022. There were 87 (85.3%) males and 15 (14.7%) females. AR gene expression was not significantly different between males and females ($p = 0.5$), whereas androgen response signature was significantly higher in male ($p = 0.03$). The AR gene expression and androgen response signature scores were more highly expressed in luminal tumors vs rest of molecular subtypes ($p = 0.005$ and $p < 0.001$). Despite AR gene expression was not associated with ypT0N0 response ($p = 0.425$), hallmark androgen response signature scores were significantly lower in ypT0N0 responders ($p = 0.033$). Higher hallmark androgen response signature scores were statistically significantly associated with shorter EFS ($p = 0.028$), whereas AR gene expression was not ($p = 0.152$). **Conclusions:** For the first time to our knowledge, we reported the androgen response pathway expression to be a potential biomarker of ICI benefit in MIBC. This signature was also associated with a luminal subtype, linked to inferior responsiveness to ICI. If confirmed at a larger scale these analyses will strengthen the need for sex-specific approaches and potentially new combination therapies in MIBC. Research Sponsor: None.

Comprehensive analysis of targetable alterations in urachal cancer by NGS.

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Background: Urachal cancer (UrC) is a rare genitourinary cancer with molecular drivers commonly found in colorectal cancer and harbors fewer actionable alterations. Although prior studies have identified genomic alterations associated with UrC, these lack comprehensive genomic profiling, often using targeted panels, and lack RNA interrogation. This study presents detailed characterization of molecular profiles and the tumor microenvironment of real-world UrC patient samples. **Methods:** UrC samples (n = 42) were profiled using next-generation sequencing (NGS) of DNA and RNA. Prevalence was calculated for pathogenic SNVs/Indels and copy number amplifications, dMMR/MSI status assessed by IHC and NGS, PD-L1 expression measured by IHC, and TMB-H defined as ≥ 10 mut/Mb. Immune cell fractions of TME were estimated using RNA deconvolution. Mann-Whitney U, chi-square, and Fisher exact tests were applied where appropriate, with *p*-values adjusted for multiple comparisons. Histological features were reviewed by a genitourinary pathologist. **Results:** UrC samples were collected from 19 males and 23 females with a median age at sample collection was 58.5 years (range: 24-86 years). Pathology review revealed the majority were adenocarcinomas (n=41/42, 97.6%), including mucinous (n=17/41, 41.5%) and enteric adenocarcinomas (n=10/41, 24.4%). Pathogenic variants were most commonly observed in *TP53* (n = 35, 83.3%), *KRAS* (n=15, 36%), *GNAS* (n=5, 12%), *SMAD4* (n=4, 10%), *PIK3CA* (n=4, 10%), *STK11* (n=3, 7%), *BRCA2* (n=3, 7%), *ARID1A* (n=2, 5%), *PTEN* (n=2, 5%), *ERBB2* (n=2, 5%), *BRAF* (n=2, 5%), and *APC* (n=2, 5%). MAPK pathway alterations were present in 52.3% (n=22) overall, with increased MAPK pathway activation in MAPK-altered UrC (median MPAS: 0.77 vs -0.61, $p = 0.066$). Loss of heterozygosity was prevalent (n = 9, 29%). While no UrC tumors had dMMR/MSI, 5% (n=2) were TMB-H and 9% (n=3) were PD-L1+. The mean fraction of T cells – CD8 (0.4%) and monocytes (0.0%) represented a smaller fraction UrC TME composition compared to macrophages M1 (5.19%) and neutrophil (6.4%). The median NK cell fraction was significantly higher in MAPK-altered UrC patients (3.5 vs 2.7%, $p = 0.022$), yet a transcriptional signature of response to immunotherapy (IFN-g) was similar between MAPK-altered and MAPK-WT UrC patients (median IFN: -0.366 vs -0.384, $p = 0.052$). **Conclusions:** This study provides a comprehensive molecular characterization of UrC and the associated immune landscape. While MAPK and DNA repair gene alterations were common, UrC tumors rarely harbored predictive markers of response to immunotherapy, suggesting limited efficacy in this patient population. However, the recurrence of MAPK alterations and associated pathway activation in UrC warrants further investigation of MAPK-targeted therapies in prospective clinical trials. Research Sponsor: None.

Activity of antibody-drug conjugates (ADCs) with radiation in preclinical bladder cancer models.

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Background: Antibody-drug conjugates (ADCs) are a novel class of therapeutics that combine a tumor cell targeting antibody with a cytotoxic payload. Two ADCs are currently approved in the US for treatment of advanced bladder cancer: enfortumab vedotin (EV) and sacituzumab govitecan (SG). Radiation therapy (RT) plays a central role in trimodality therapy (TMT), a curative treatment approach for muscle-invasive bladder cancer (MIBC). However, the biological activity of ADCs combined with RT in preclinical MIBC models has not been reported. **Methods:** We use a molecularly annotated panel of human MIBC preclinical models to test the impact of RT on expression of ADC targets and define the combined activity of EV and SG with RT. We also test the *in vivo* activity of combining ADCs with image-guided, fractionated RT in bladder cancer flank xenograft mouse models. **Results:** Radiation has variable impact on expression levels of nectin-4 and trop-2, the targets of EV and SG, respectively, as determined by immunoblot, immunofluorescence microscopy, and immunohistochemistry (IHC). Whereas modest dose-dependent increases in nectin-4 and/or trop-2 levels were observed in some models, no significant changes were observed in other models. Importantly, RT did not lead to a significant decrease in nectin-4 or trop-2 expression in any of the models. EV and SG showed additive or synergistic cell killing when combined with RT across preclinical models *in vitro*. Combining EV or SG with fractionated RT *in vivo* was well-tolerated, showed improved tumor control, and prolonged survival in bladder cancer flank xenograft mouse models compared to either ADC or RT alone. **Conclusions:** ADCs demonstrate combination activity with RT across a panel of molecularly diverse bladder cancer preclinical models. These studies provide preclinical data supporting clinical trials to investigate the safety and efficacy of combining ADCs with RT as a bladder-preserving therapy for MIBC. Research Sponsor: None.

Impact of homologous recombination repair (HRR) or nucleotide excision repair (NER) deficiency on sensitivity to antibody drug conjugate (ADC) payloads in urothelial cancer.

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Background: Approximately 10% of urothelial cancer (UC) patients have defects in the NER pathway and at least another 10% have defects in the HRR pathway. Tumors with HRR or NER defects are more sensitive to platinum-based chemotherapy due to inability repair platinum-induced DNA damage. Two ADCs, sacituzumab govitecan (SG) and enfortumab vedotin (EV) are approved for treatment of metastatic UC. The cytotoxic payload attached to SG and EV are SN-38 and MMAE respectively. SN-38 directly damages DNA through inhibition of Topoisomerase 1 activity during DNA replication whereas MMAE is a potent microtubule disruptor but does not have any direct DNA damaging effects. Given the expanding clinical roles for EV and SG in UC, we wished to test the impact of HRR or NER deficiency on sensitivity to SN-38 and MMAE. We hypothesized that HRR or NER deficiency would result in a larger increase in sensitivity to SN-38 than MMAE. We also hypothesized that SN-38, but not MMAE, would result in synergistic cell killing when delivered with a PARP inhibitor. **Methods:** We assembled a series of isogenic NER- and HRR-proficient/deficient cell pairs and compared sensitivity to SN-38 and MMAE, as well as other clinically relevant agents including cisplatin, gemcitabine, and the PARP inhibitors olaparib and talazoparib. **Results:** HRR-deficient bladder cancer cell lines were significantly more sensitive to SN38 than their respective isogenic HRR-proficient counterpart whereas there was no significant difference in MMAE sensitivity between isogenic pairs of HRR-deficient and HRR-proficient cell lines. The largest difference in sensitivity between HRR-proficient vs HRR-deficient cell lines was observed with olaparib and talazoparib respectively. In contrast, NER-deficient cell lines were not more sensitive to SN38 or MMAE than their respective isogenic NER-proficient counterparts. **Conclusions:** HRR deficiency significantly increases sensitivity of bladder cancer cells to SN-38 but not MMAE. These findings suggest that UC patients with HRR deficiency may be more likely to benefit from treatment with SG than EV, and more generally with an ADC that has a Topoisomerase 1 inhibitor rather than a microtubule disruptor as the cytotoxic payload. Research Sponsor: None.

Pulsed electromagnetic field therapy's effect on bladder cancer cell line HT-1376.

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Background: Pulsed electromagnetic field therapy (PEMF) is a magnetic waveform energy that can be targeted for delivery to cells and/or patients. It is noninvasive, and to date no reported negative side effects exist. Recently, its use as a therapeutic for cancer has come into focus. However, to our knowledge, no study has examined the effect of PEMF on bladder cancer at the cellular level. In this study, we sought to examine how PEMF altered a bladder cancer cell line (HT-1376) at the genomic level. **Methods:** HT-1376 cells were cultured, and cells were plated into either a control plate (no PEMF) or experimental plate (PEMF). The experimental cells were subjected to PEMF which had an oscillating magnetic field ranging from 1.5 MilliTesla (mT) to 16 mT at 30 Hertz, 1 hour each day for 3 total days. RNA was isolated from both control and experimental cell plates on day 3 and assayed on whole genome microarrays. Day 3 control samples from HT-1376 were compared to day 3 PEMF treated cells. Results were analyzed using Ingenuity Pathway Analysis. **Results:** Data from genomic analysis revealed that many cancer-related pathways were altered after treatment with PEMF in HT-1376. Relevant cancer pathways downregulated after PEMF treatment in HT-1376 cells compared to controls were the PIK3/AKT pathway (p=8.1e-61), neuroinflammation signaling pathway (p=2.3e-60), and external growth factor pathway (p=4.8e-35). Upregulated pathways after PEMF treatment relative to controls were the p53 signaling pathway (p=1.1e-06), endocannabinoid cancer inhibition pathway (p=1.1e-38), and the T-cell exhaustion signaling pathway (p=3.7e-22). The table also lists cancer relevant genes up and downregulated after PEMF treatment. **Conclusions:** PEMF appears to alter the tumor profile of bladder cancer cell line HT-1376. Key pathways implicated in cancer pathogenesis were altered after treatment. Further, after treating HT-1376 bladder cancer cells with PEMF for 3 days, significant alterations in gene expression occurred. This has widespread implications for prognosis, management, and treatment of bladder cancer. Ultimately, PEMF may represent an exciting new non-invasive therapeutic in bladder cancer, which necessitates further research. Research Sponsor: None.

Cancer related gene alterations after PEMF treatment.

Gene	Fold Change	Role
TP53	8.8	Tumor suppressor
CDKN1A	1.8	Halts cell cycle
Rb1	3.3	Tumor suppressor
CCL19	-1.5	Promotes tumor invasion
VEGFA	-1.6	Angiogenesis

Each fold change represents a specific gene up/downregulation in PEMF treated cells relative to controls. A positive fold change is upregulation and negative is downregulation.

Outcomes with sacituzumab govitecan (SG) in patients (pts) with advanced urothelial carcinoma (aUC) and variant histologies (VH): Analysis of the UNITE study.

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Background: SG is approved in pts with aUC refractory to platinum-based chemotherapy (PBT) and checkpoint inhibitor therapy (CPI). Data on SG outcomes in pts with subtype/variant histologies (VH) are limited. We examined SG-treated pts in the UNITE study and hypothesized that outcomes would be similar between pts with pure urothelial histology (pUC) and any VH component. **Methods:** UNITE is a multi-site retrospective study of pts with aUC treated (Tx) with targeted agents, such as enfortumab vedotin (EV) and SG. Pts who received SG monotherapy were included in this analysis. Observed response rate (ORR) was assessed by investigators at each site for evaluable pts with scans after ≥ 1 SG cycle using χ^2 and logistic regression. Progression-free and overall survival (PFS, OS) from SG start were assessed using KM method and Cox proportional hazards model. **Results:** Among 633 total pts in UNITE, 116 received SG monotherapy at 11 US sites. Median age was 70; 79 (68%) male; 97 (84%) Caucasian; 86 (74%) ECOG PS 0/1; 84 (72%) lower tract tumor; 90 (78%) visceral or bone mets; 48 (41%) Bellmunt score ≥2; 72 pts (62%) had pUC and 44 (38%) VH, including 33 (28%) with UC predominant (<50% VH) and 11 (9%) with variant predominant (≥50% VH). For prior therapy, 109 pts (94%) received >2 prior lines; 75 (65%) PBT; 102 (88%) CPI; 109 (94%) EV. Median time from metastatic diagnosis to SG start was 18.6 months (mo) (0.9-84.5). Median follow up from SG start was 10.6 mo (8.5-15.4). Median time on SG was 1.6 mo (0.2-14.7). ORR to SG was 24% (20/84); median PFS and OS from SG start were 3.7 mo (95% CI 3.0-4.6) and 6.7 mo (95% CI 5.3-10.8). VH (n ≥1) included: squamous (SQH) (19, 16%), micropapillary (9, 8%), plasmacytoid (8, 7%), adenocarcinoma (3, 3%), neuroendocrine (NE) (2, 2%). In evaluable pts with VH, ORRs: squamous (3/14), micropapillary (1/4), plasmacytoid (0/6), adenocarcinoma (2/3), NE (1/2). No significant differences were observed in outcomes between pUC and any VH or pUC and SQH (Table). **Conclusions:** Pts with aUC treated with SG appear to have similar clinical outcomes between pUC and any VH. Responses to SG are observed across different VH. Limitations include low power, tumor heterogeneity, lack of central pathology/scan review, selection and confounding biases. These hypothesis-generating findings suggest activity of SG post-PBT, CPI, and EV in pts with VH, but should be validated in larger cohorts with adequate sample size of specific VH and longer follow up. Research Sponsor: None.

	Pure Urothelial (pUC) N=72	Any Variant Histology (VH) N=44	Any Squamous Histology (SQH) N=19	pUC vs VH	pUC vs SQH
ORR	24% (13/54)	23% (7/30)	21% (3/14)	OR: 0.96 p=0.94	OR: 0.86 p=0.84
mPFS: mo (95% CI)	3.5 (2.3-4.8)	3.7 (3.2-6.0)	3.2 (1.8-12.4)	HR 0.84 (95% CI 0.54-1.31) p=0.44	HR 1.01 (95% CI: 0.56-1.82) p=0.98
mOS: mo (95% CI)	6.7 (5.3-11.5)	6.2 (4.4-NR)	5.3 (3.2-NR)	HR 0.99 (95% CI 0.59-1.63) p=0.96	HR 1.36 (95% CI: 0.71-2.59) p=0.35

The potential of transcriptomic profiling to predict immune-checkpoint inhibitor (ICIs) response in locally advanced (La) and metastatic urothelial carcinoma (mUC).

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Background: Immune checkpoint inhibitors (ICIs) have proven to be an effective therapy for locally advanced (La) and metastatic (mUC) urothelial carcinoma. However, response rates are typically modest, and patient (pt) selection remains a challenge, especially in the era of ICIs-based combos. The current study analyzes the differential RNA expression as a predictor of ICI response or resistance in La/mUC. **Methods:** Clinical information and formalin-fixed paraffin embedded (FFPE) samples from pts with La/mUC treated with single agent ICIs [2014 -2021] were obtained and RNA sequencing (RNA-seq) analysis performed. According to response, pts were assigned to one of these three groups: Primary resistant [PR] (progressive disease (PD) as the best response); Secondary resistant [SR] (initial response followed by PD); and Long responders [LR] (stable disease/partial or complete response maintained $>$ 16 months). **Results:** Clinical data and FFPE samples from 46 patients were available. Nineteen, twelve and fifteen pts respectively were in the PR, SR and LR groups. Clinical characteristics were well-balanced among groups, except for higher percentage of liver metastasis in PR and SR pts. The median overall survival was 11.2 and 18.2 months for the PR and the SR groups and has not yet been reached for the LR cohort, where 80% of the pts remain alive, with 50% achieving complete response. RNA-seq analysis unveiled distinct patterns of differential gene expression in the resistance groups compared to the LR. Notably, an upregulation of the epithelial-mesenchymal transition pathway was observed, with interleukin 2 emerging as a potential surrogate marker of this activity. Additionally, an overactivation of the KRAS pathway was evident, irrespective of its mutational status. Furthermore, in a comparison between the two resistance groups, the SR group displayed increased activation of DNA damage control mechanisms. **Conclusions:** Our RNA-seq analysis could provide relevant information and holds promise as a valuable tool for predicting responses to ICIs in La-mUC. Nonetheless, further validation on a larger cohort of patients is required. Research Sponsor: Roche-Spain.

The impact and mechanisms of gut microbiota on the efficacy of neoadjuvant therapy in patients with MIBC.

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Background: Platinum-based neoadjuvant chemotherapy, such as gemcitabine/cisplatin (GC) or dose-dense methotrexate/vinblastine/doxorubicin/cisplatin (ddMVAC), followed by radical cystectomy (RC), represents the current standard of care for T2-T4aN0M0 muscle-invasive bladder cancer (MIBC). Regrettably, only 40% of patients who received neoadjuvant chemotherapy achieved a pathological complete response (pCR). Recently, several trials showed a promising efficacy of immune checkpoint inhibitors (ICIs) plus neoadjuvant chemotherapy. BGB-A317-2002 study indicated that the addition of tislelizumab to GC can increase the pCR rate to 54.5%, with a pathological downstaging rate of 77.3%. Nevertheless, a subset of patients failed to derive benefits from ICIs plus neoadjuvant chemotherapy. **Methods:** This study aimed to explore the impact and mechanisms of gut microbiota on the efficacy of neoadjuvant therapy through the analysis of fecal samples obtained from MIBC patients who received GC or GC plus ICIs. Here, we reported the impact of gut microbiota on treatment outcomes in patients who received GC. **Results:** A total of 54 patients who received neoadjuvant GC chemotherapy were enrolled. Among them, 23 (42.59%) exhibited a pathological response (responsive group), and 31 (57.41%) showed no response (non-responsive group; no imaging changes or disease progression). Metagenomic sequencing on fecal samples from patients before and after therapy showed that the Shannon index in species level (1.182 vs. 0.954, p=0.016) and abundance of *Ruminococcus gnavus* were significantly greater in the responsive group than non-responsive group. It suggested that responsive patients displayed higher species richness of gut microbiota. **Conclusions:** The efficacy of neoadjuvant GC chemotherapy in MIBC patients may be potentially influenced by the number of gut microbiota populations. Additionally, the potential application value of *Ruminococcus gnavus* in improving the efficacy of non-responsive patients is noteworthy. A larger-scale study is needed to determine the above findings. Research Sponsor: None.

Genomic correlates of response and resistance to immune checkpoint inhibitors (ICI) in patients with metastatic urothelial carcinoma (mUC) in a real-world setting.

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Background: Response rates with ICI are only about 20% in mUC and we lack validated biomarkers to select patients who are most likely to derive benefit from ICI. Programmed cell death ligand 1 (PD-L1) has not proven to be a useful biomarker. We need biomarkers of response and resistance to avoid nonbeneficial treatment (Tx) and spare the majority of pts who will not respond to ICI both physical and financial toxicity. Here we report tumor genomic correlates of response and resistance to ICI in pts with mUC. **Methods:** We identified 335 adult pts with mUC at the Cleveland Clinic treated who received > / = 2 cycles of ICI with pembrolizumab (P) or atezolizumab (A) between 2015 and 2023. Of the 335 pts, 49 had pre-Tx archival formalin fixed paraffin-embedded (FFPE) tissues available. Pts were categorized by their response to ICI as responders (R) (Complete Response (CR), Partial Response (PR), and Stable Disease (SD)) (N = 23) or non-responders (NR) (Progressive Disease (PD)) (N = 26). Whole exome sequencing was performed from macro dissected tumors. Raw data in FASTQ format was aligned to GRCh38 human reference genome, somatic mutations were called by Mutect2 (part of GATK4) and allele-specific copy-number analysis was performed by applying the Facets and Gistic2 package. **Results:** Comparison of our cohort Tumor Mutation Burden (TMB) with mutation burden of 33 the cancer genome atlas (TCGA) cohorts shows close similarity to TCGA bladder urothelial carcinoma (BCLA). Median TMB in our cohort was 6.46 muts/Mb. In our cohort, TP53 hotspot mutations were found in 52% of the (R) cohort compared to 31% in the (NR) cohort. Additionally, mutations in KMT2C and KMT2A were found in 26% and 22% of the (R) cohort compared to 8% and 12 % of the (NR) cohort. (R) also had increased mutations in the ARID1A (17% vs 4%) and ERBB2 (17% vs 4%) compared to (NR). FGFR3 missense mutations were seen in only 4% of (R) cohort compared to 15% in (NR). In our complete cohort, 49% of patients had ERBB2 copy number amplifications and 92% of patient had CREBP2 deletions. **Conclusions:** In our real-world cohort of mUC pts treated with ICI, we identified differential genomic alterations between (R) and (NR). High frequency of ERBB2 mutations and alterations in overall cohort and higher frequency in (R) suggests potential role for anti-HER2 therapies alone or in combination with ICI. Ongoing genomic and immunologic correlative studies in our cohort will further help understand biomarkers of response and resistance to ICI in pts with mUC. Research Sponsor: None.

Applying fragmentomics profiles of urinary cell-free DNA for bladder cancer detection.

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Background: The liquid biopsy approach focusing on DNA molecules supports non-invasive diagnosis of bladder cancer. While utilizing cell-free DNA fragmentation characteristics for the cancer detection has shown potential in plasma, its applications in urine remained unexplored. **Methods:** We enrolled 70 patients with bladder cancer and 49 healthy individuals in this study. The urinary cell-free DNA (ucfDNA) was extracted and tested by PredicineSCORE, a low pass whole genome sequencing (LP-WGS) assay to identify tumor-specific features. The ucfDNA fragmentomics profiles including the coverage at specific region, length and end-motif of fragment was implemented. We also investigated the copy number variation and the inferred tumor fraction which was adjust by the Expectation-Maximum (EM) algorithm. Subsequently, an ensembled machine learning model were constructed for classification of bladder cancer and normal control. **Results:** We observed strong correlation between tumor fraction and specific features. The absolute correlation coefficient between tumor fraction with the LYL1 bonding sites relative depth, the insert size ratio of short reads, and the CCCA end motif were above 0.9, 0.75 and 0.7, respectively. To further assess the robustness of PredicineSCORE assay, we then diluted the tumor samples with tumor fraction ranging from 0.1% to 50% by manually mix reads from tumor samples into normal samples. By applied XGBoost algorithm, the performance (F1 score $>$ 0.95) showed promising ability to distinguish tumor from normal samples. The limit of detection (LOD) was less than 1%, indicating heightened sensitivity compared to previously proposed models. **Conclusions:** The study suggests that urinary cell-free DNA fragmentomic profiling may enhance the precision of non-invasive bladder cancer detection. Research Sponsor: None.

MAPK pathway alterations as a targetable vulnerability in bladder cancer.

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Background: Large-scale genomic studies of bladder cancer (BC) have identified MAPK as a recurrent pathway alteration. The MAPK pathway is a signaling cascade comprising of the proteins RAF, MEK, and ERK, which together control critical cellular processes. Currently, cisplatin-based chemotherapy and anti-PD1/PD-L1 agents are the backbone of systemic therapy in BC, yet only a subset of patients respond. As such, additional novel therapeutic strategies, such as targeting the MAPK pathway, are needed. Herein, we describe the impact of MAPK alterations on BC tumor properties sensitivity to novel MAPK-directed agents. **Methods:** The activity of the activity of RAF inhibitors (including RAF265 and the novel RAF dimerization inhibitor LXH254) was tested in BC cell lines with diverse MAPK pathway alterations including RAF1 amplification and NRAS mutations. Relative cell viability was measured by luminescence assay following treatment. RAF1-amplified UMUC9 cells were implanted as mouse flank xenografts which were randomized to treatment with vehicle or RAF inhibitor alone or in combination with a MEK inhibitor, trametinib. Mouse weights and tumor measurements were monitored during the treatment period and tumors were excised and weighed. C57BL/6 mice were orthotopically implanted with BBN cells with and without a RAF1 amplification using a surgical approach and tumor volumes were measured under ultrasound (US). **Results:** RAF1-amplified and NRAS-mutated cell lines demonstrated higher sensitivity to RAF inhibition than non-altered lines. There was a significant reduction in tumor volumes of UMUC9-engrafted mice treated with RAF265 (n=10) or RAF265 plus trametinib (n=8) compared to vehicle controls (n=14). Mice treated with RAF265 alone or with RAF265 plus trametinib had significantly lower tumor weights than vehicle-treated mice. US monitoring showed that mice orthotopically implanted with RAF1-amplified BBN cells (RAF1, n=9) and empty vector cells (EV, n=9) showed take rates [RAF1=67%, EV=78%], mean tumor sizes [RAF1=23.0mm^2, EV=12.5mm^2, p=0.07], and tumor growth rates [RAF1=0.60mm^2/day, EV=0.40mm^2/day, p=0.19]. **Conclusions:** We sought to explore the vulnerabilities incurred by MAPK pathway alterations in BC. We tested the activity of a RAF inhibitors in BC cell lines with RAF1 amplifications and NRAS mutations and found that MAPK pathway-altered models displayed increased sensitivity to RAF inhibition compared to MAPK-unaltered models. We further showed this sensitivity *in vivo* with RAF1-amplified mouse xenografts and elucidated the synergistic effect of concurrent RAF and MEK inhibition. There was a trend towards larger tumors and more rapid growth rate in orthotopically-implanted RAF1-amplified BC cells compared to controls. Taken together, these data identify MAPK pathway alterations as a novel dependency in BC that may be clinically targeted with small molecule inhibitors. Research Sponsor: None.

Occurrence of *NECTIN4* amplification in solid tumors and enfortumab vedotin response in metastatic urothelial cancer.

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Background: The anti-NECTIN4 antibody-drug conjugate (ADC) enfortumab vedotin (EV) is approved for patients with metastatic urothelial cancer (mUC). However, durable benefit is only achieved in a small, yet uncharacterized patient subset. *NECTIN4* is located on chromosome 1q23.3, and 1q23.3 gains are frequent genomic events in mUC leading to *NECTIN4* amplifications. Here, we aimed to evaluate the potential of *NECTIN4* amplification as a genomic biomarker to predict EV response in patients with mUC. **Methods:** We established a *NECTIN4*-specific fluorescence in-situ hybridization (FISH) assay to assess *NECTIN4* copy number variations (CNVs) in a multicenter EV-treated mUC patient cohort (UC-EV, N=77), and CNV data were correlated with membranous NECTIN4 protein expression (H-score) assessed via immunohistochemistry, EV treatment responses and outcomes. Next, we conducted a pan-cancer analysis of the The Cancer Genome Atlas (TCGA) datasets, comprising 10,712 patients across 32 cancer types, to investigate the relationship between *NECTIN4* CNV, mRNA expression (RNAseq) and protein levels (RPPA) across entities. **Results:** In TCGA cohorts, *NECTIN4* amplification occurs frequently across different solid cancer types, especially in 15-20% of bladder cancers (17% in TCGA-BLCA), as well as 5-10% in breast cancer (TCGA-BRCA) and lung adenocarcinoma (TCGA-LUAD). We confirmed the amplification frequency in our UC-EV cohort (18%). *NECTIN4* amplification is significantly associated with both increased *NECTIN4* mRNA expression (e.g., TCGA-BLCA, BRCA, LUAD) and membranous NECTIN4 protein expression (UC-EV), and represents a stable genomic alteration during metastatic progression. In the UC-EV cohort, all patients with *NECTIN4* amplification (N=14) responded to EV. In multivariable Cox adjusted for age and sex, *NECTIN4* amplifications led to a 93% risk reduction for death compared to a *NECTIN4*non-amplified status (HR=0.07, 95%-CI 0.01–0.53; $P<0.001$). **Conclusions:** Our study highlights the value of *NECTIN4* amplifications to predict EV responses in patients with mUC. *NECTIN4* amplifications occur frequently in different cancer types and therefore have the potential to be a novel tumor-agnostic genomic biomarker that enables tailored NECTIN4-targeted therapies in various entities. Research Sponsor: Medical Faculty of the University of Bonn; Deutsche Forschungsgemeinschaft; Else Kröner-Fresenius Foundation.

Application of artificial intelligence (AI) features of nuclear morphology from BLASST-1 (Bladder Cancer Signal Seeking Trial) of nivolumab, gemcitabine, and cisplatin in patients with MIBC undergoing cystectomy.

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Background: BLASST-1 is a multi-center phase II trial evaluating neoadjuvant nivolumab (N) with gemcitabine-cisplatin (GC) for patients (pts) with MIBC undergoing radical cystectomy (RC) (NCT03294304). 41 pts with MIBC (cT2-T4a, N≤1, M0) were enrolled between Feb 2018 and June 2019; (cT2N0 90%, cT3N0 7%, cT4N1 3%). Pts received C (70mg/m2) IV on D1, G (1000mg/m2) on D1, D8, and N (360 mg) IV on D8 every 21 days for 4 cycles followed by RC within 8 wks. The primary endpoint was pathologic downstaging (PaR; ≤pT1N0). Safety, Relapse-free survival (RFS), Progression-free survival (PFS) and biomarker analyses were secondary endpoints. PaR rate was 65.8%, the pCR (≤pT is N0) rate was 49% and there were no safety concerns or delays to RC. Morphometric characteristics of the cell nucleus can be used to assess bladder cancer grading and gain insights into cellular functionalities. In this study, we sought to evaluate the ability of the AI model to identify non-responders to neoadjuvant chemo-immunotherapy. in the BLASST-1 cohort based on computerized image features of nuclear morphology and architecture on pre-treatment transurethral resection of bladder tumor (TURBT) tissues. **Methods:** Of the 41 pts, we had H&E images available for 34 pts, of which 23 had PaR and 11 did not have PaR and these were classified as responder (R) and non-responder (NR) groups. A machine learning model (U-net) was developed and invoked for tumor segmentation on the H&E images from the BLASST-1 cohort. A second machine learning model (HoVer-Net) was employed to segment and classify individual nuclei. A total of 408 features relating to the textural and spatial arrangement of individual cancer nuclei were extracted. The 17 most significant features, identified through the least absolute shrinkage and selection operator, were used to train a Cox regression model to predict the risk of death using 361 MIBC pts from the Cancer Genome Atlas (TCGA). This Cox model was then applied to assign a risk score to pts in BLASST-1, using a threshold learned from TCGA pts, the individual pts in BLASST-1 were assigned as either low-risk or high-risk. **Results:** The top identified prognostic features described the textural appearance of individual nuclei with more texture. This model accurately predicted PaR in BLASST-1, with an area under a receiver operating characteristic curve of 0.83. Overall, the pts with the same nuclear angle direction within the tumor tissue had a high chance of response to the neoadjuvant chemo-IO combination in the BLASST-1 trial. **Conclusions:** A computerized AI model relying on nuclear morphologic and architecture features demonstrated prognostic capability in MIBC within the TCGA dataset and predictive capability for the PaR in the BLASST-1 trial. These findings support further validation studies. Research Sponsor: None.

675 Poster Session

Differential mutation profiles between benign and cancerous urothelium in patients with non-muscle invasive bladder cancer (NMIBC).

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Background: Differentiating passenger and driver mutations of oncogenesis is essential in understanding disease biology and developing biomarkers that use genomic mutations for diagnosis or prognostication. Accumulating research shows normal urothelium harbors many mutations commonly reported in molecular profiling of urothelial carcinoma. This is especially true of NMIBC. Here, genetic profiling of the mutational landscape of pathologic NMIBC tumors (pNMIBC) was performed and compared to matched pathologically benign urothelial tissue (pBT) to determine the frequency of passenger mutations. **Methods:** From a prospective observational cohort, 9 patients with high-risk NMIBC and pBT on repeat TURBT were identified. Somatic mutational profiles of the index tumor (pNMIBC) and subsequent pBT of each patient was performed via PredicineWES+ whole exome sequencing. Somatic variants were identified using the Predicine DeepSea in-house algorithm as previously described. Briefly, non-synonymous variants are captured and probabilistically annotated as germline vs. somatic in comparison with matched germline PBMC WES+ sequencing. NS somatic mutations observed in pBT were compared to those in pNMIBC to evaluate for putative passenger versus driver mutations. **Results:** A median of 236 mutations (IQR:100-732) were detected for pNMIBC compared to 37 (IQR: 5-80) in the pBT group (p=0.018). The number of genes with likely somatic mutations in pNMIBC only, both samples, and pBT only, were 2239, 500, and 1, respectively. The most frequently mutated genes in pNMIBC tissue samples were *ARID1, TERT, CREBBP, LMTK3* and *NCOR1*. Notably, both pBT and pNMIBC tissue shared mutations in commonly reported bladder cancer genes such as *ARID1A, ERBB2, ATM, ERCC2* and *CKDN2A.* Somatic mutations in *FGFR3, LMTK3, NCOR1, AKAP9, COL11A2, CRYBG3, KMT2A, MCM3AP, PHF3, VPS13A* and *ZNF28* were present solely in pNMIBC tissue, whereas *OVGP1* mutation was exclusive to pBT. Analysis of the functional impact of mutations in genes that are mutated in both benign tissue and pNMIBC offers a deeper understanding of the evolution of bladder cancer via field cancerization. **Conclusions:** Analysis of the mutational profile of pBT and pNMIBC revealed differential patterns of somatic mutations. Many expected gene mutations were detected in pNMIBC, but surprisingly 18% of all mutated genes were shared between tumor and pathologically benign samples. The fact that only one somatically mutated gene was exclusive to pBT signifies excellent censoring of variants by the DeepSea algorithm. In summary, these preliminary findings suggest that common gene mutations in NMIBC are frequently observed as passenger mutations. This underscores the potential significance of tissue-informed biomarkers tailored to an individual's mutational profile, which may outperform panel assays. Research Sponsor: Predicine Inc.

Urine-based testing for patient selection and genomic characterization of patients with *FGFR* alteration-positive non–muscle-invasive bladder cancer (NMIBC) treated with TAR-210.

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Background: TAR-210 is an intravesical drug delivery system that is designed to provide local, continuous release of erdafitinib. Its safety and efficacy are being evaluated in a first-in-human clinical study (NCT05316155) of patients with bladder cancer whose tumors harbor select *FGFR* alterations (alt). Toovercome tissue-based challenges in identifying susceptible *FGFRalt* to select patients for treatment with TAR-210, Janssen partnered with Predicine to use a proprietary urine cell-free DNA diagnostic assay (PredicineCARE). Validation of the urine assay to detect *FGFRalt* was previously demonstrated using urine samples collected in a highly controlled manner via a collaboration with Stratifyer Molecular Pathology GmbH, Cologne, Germany (Kim et al. ASCO GU 2023). However, evaluation of the urine assay for diagnostic screening in a real-world setting is currently lacking. Here, we report preliminary results of the urine assay for patient selection. We also report on the characterization of the urine-defined genomic landscape in screened patients. **Methods:** Enrollment was based on detection of prespecified *FGFRalt* from either tumor tissue obtained from previous biopsies (Qiagen Therascreen FGFR assay) or urine samples obtained prior to enrollment (PredicineCARE next-generation sequencing assay). **Results:** As of Jun 20, 2023, urine assay performance was compared to the tissue test from all screened patients with NMIBC (N=178). The proportions of samples that yielded results were 60% and 58% from tissue and urine, respectively, while the *FGFR*alt detection rates in the subsets that yielded results were 62% and 42%, respectively. *FGFR3* S249C was the most frequent alteration detected in both tissue (48%) and urine (61%). For 36% of urine samples in which *FGFR*alt were detected, there was no corresponding tissue result. Of the disease-evaluable patients with high-risk (HR) NMIBC (N=11) or intermediate-risk (IR) NMIBC (N=15),18.2% and 33%, respectively, were enrolled based on urine assay alone due to insufficient tissue samples. A recurrence-free (RF) rate of 82% and a complete response (CR) rate of 87% were achieved at the first disease evaluation amongst patients with HR NMIBC and IR NMIBC, respectively. All patients (HR NMIBC, N=2, and IR NMIBC, N=5) enrolled by "urine only" were RF or achieved a CR. Based on the PredicineCARE panel, comprehensive genomic assessment of urine samples from all screened patients with NMIBC was performed. The prevalence of alterations detected was similar to that described in prior studies using tissue-based testing. **Conclusions:** Implementing a urine-based assay expands the molecular testing methods to identify additional patients that may respond to erdafitinib. Results justify further study. Clinical trial information: NCT05316155. Research Sponsor: Janssen Research & Development.

Blood-based liquid biopsy: A promising non-invasive test in diagnosis, surveillance, and prognosis of patients with upper tract urothelial carcinoma.

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Background: Blood-based liquid biopsy has emerged as a novel biomarker to improve the diagnosis and monitoring of urothelial tumors while enabling individualized risk stratification. The aim of this study was to assess the efficacy of these novel biomarkers in the diagnosis, surveillance, and prognosis of patients with primary upper tract urothelial carcinoma (UTUC). **Methods:** In this prospective study, peripheral blood samples were collected from patients with primary UTUC before surgery with curative intent and follow-up visits between May 2021 and September 2022. The samples were analyzed using the third-generation comprehensive high-definition single-cell assay (HDSCA3.0) to detect rare events, including circulating tumor cells (CTCs) and oncosomes, based on the immunofluorescent signals of DAPI (D), cytokeratin (CK), CD45/CD31 (CD), and vimentin (V). The findings of pre-surgery liquid biopsies were compared to the blood samples of normal donors (NDs) and matched follow-up liquid biopsy samples. The association between liquid biopsy findings and clinical data elements, including progression-free survival (PFS), was also assessed. **Results:** Twenty-eight patients with a median (range) age of 67.5 (43-88) years were included, of whom 21 had follow-up samples. Pathologic staging revealed 15 pT<2 and 13 pT≥2 tumors, and most cases (23/28) were high-grade.Significant differences in specific rare analytes were detected in pre-op samples as compared to NDs. On the post- vs. pre-surgery matched analysis, a significant decrease was detected in total-, CK-, and CK|V oncosomes as well as D-, D|V-, and D|V|CD cells. Correlation between pre-surgery liquid biopsy findings and clinical data is shown in Table 1. With a median follow-up of 11 months, seven patients had disease recurrence. Survival analysis demonstrated that patients with greater than 1.95 preoperative CK|V oncosomes as well as those with greater than 4.18 D|CK|V cells had worse PFS compared to other patients (p=0.02 and p=0.05, respectively). **Conclusions:** This study demonstrates promising initial evidence for biomarker role of CTCs and oncosomes in diagnosis and surveillance of patients with UTUC. Research Sponsor: USC Urology Research Council.

Clinical correlations between pathological variables and liquid biopsy findings.

Clinical Variables			Liquid Biopsy Variables*			
Variable	**Group 1**	**Group 2**	**Variable**	**Group 1**	**Group 2**	**p-value**
Concomitant CIS	No	Yes	D|V|CD cell	38.2	194.4	0.021
LVI	No	Yes	D|CK cells	0.7	7.1	0.017
LVI	No	Yes	CK Oncosome	8.6	16.9	0.025
pTstage	T1	T3	D|V cell	0.8	76.3	0.028
pTstage	T1	T3	Total Cells	16.4	220.8	0.045
pTstage	T1	T3	Total Counts	19.9	230.7	0.045

CIS: carcinoma in situ; LVI: lymphovascular invasion. * Reported as cells/oncosomes per mL.

Effect of neutrophil to lymphocyte ratio (NLR) on outcomes with immune checkpoint inhibitors (ICIs) in patients (pts) with metastatic urothelial carcinoma (mUC) in real-world setting.

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Background: Elevated inflammatory biomarkers like the neutrophil to lymphocyte ratio (NLR) has been associated with poor prognosis in several cancers, including UC but there is limited evidence on its role as a prognostic biomarker in patients (pts) with mUC treated with ICIs. We studied the effect of baseline (pre-treatment) NLR on outcomes with ICI in mUC pts in our large cohort of patients with mUC treated with ICIs. **Methods:** We identified 335 adult pts with mUC at the Cleveland Clinic treated who received >/= 2 cycles of ICI with pembrolizumab (P) or atezolizumab (A) between 2015 and 2023. Patient characteristics including age, sex, race, primary site (bladder vs upper tract UC (UTUC)), tumor histology and pre-ICI treatment NLR values were collected and divided into four quartiles: (NLR <2.7, 2.7-4.0, 4.0-7.1, and >7.1). Impact of NLR on overall survival (OS) and progression free survival (PFS) post ICI start date was studied. OS and PFS were estimated using the Kaplan Meier method and compared by log rank test. **Results:** Of the 335 pts, NLR values were available for 320 pts. Median age was 73 yrs (35-95) and 76% pts were males. 247 pts (74%) received P and 88 (26%) received A. We found that in the 320 patients with available NLR values, the highest quartile values of NLR >/= 7.1 was significantly associated with worse OS (p=0.01). We did not find a statistically significant impact of NLR on PFS (p=0.06). (Table). **Conclusions:** In our large real-world cohort of pts with mUC receiving ICI, we report the effect of baseline NLR on outcomes with ICI and that NLR >/=7.1 was associated with significantly worse OS. Further validation studies are warranted to risk-stratify pts with mUC planned for ICI treatment. Research Sponsor: None.

NLR	N	Median OS mos (95% CI)	Median PFS mos (95% CI, p value)
<2.7	75	19.75 (13.08, 28.39)	6.21 (4.01, 9.56)
(2.7-4.0)	82	15.57 (11.99, 21.91)	6.41 (4.83, 10.81)
(4.0,7.1)	82	12.06 (7.59,22.83)	4.48 (3.29, 6.28)
>=7.1	81	7.59 (5.22,14.00)	4.11 (2.60, 5.62)

Comparison of tissue based FGFR mutation detection by Therascreen FGFR with UroTyper FGFR and ADC test and relevance for potential co-targeting with TROP2 and NECTIN4: Preview of Bladder BRIDGister.

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Background: In view of the efficacy of FGFR targeting in early and advanced bladder cancer, as has been shown for erdafitinib in the THOR and NORSE trial, molecular testing of FGFR mutations and fusions will soon become clinical routine worldwide. Therascreen FGFR testing has been approved as companion diagnostic to select patients for erdafitinib. However, technical problems and shortages as well as a limited number of detectable mutations indicate the need of FGFR test systems that can be performed easily & fast worldwide. The objective was to evaluate concordance of UroTyper FGFR with Therascreen FGFR mutation testing and unravel molecular characteristics of FGFR mutated tumors to assess potential co-targeting options for erdafitinib to justify subsequent adopted clinical trials with the Bladder BRIDGister framework. **Methods:** FFPE tumor tissues from 100 TURB samples were prospectively collected as part of the Bladder BRIDGister. RNA from FFPE tissues were extracted by commercial kits to assess Therascreen FGFR & UroTyper FGFR MODAPLEX (BIOTYPE GmbH, Dresden) in conjunction with relative gene expression of subtyping markers (i.a.. PPARG), ADC targets (TROP2, NECTIN4) and CPI targets by RT-qPCR systems. Hierarchical clustering, Spearman correlation tests were done by JMP 9.0.0 (SAS software). **Results:** After exclusion of FGFR fusion samples, a total of 94 samples was available for comparative mutation analysis. Both PCR based FGFR tests concordantly identified S249C (n=15), R248C (n=2) and G370C (n=1) mutations, while the results for Y373C were in part discrepant with Therascreen FGFR detecting 9 mutations, while UroTyper FGFR did detect 6 mutations. Further examination of the 3 discrepant Y373C cases by SNaPshot and Uromonitor FGFR test revealed that the Therascreen FGFR test resulted in 3 false positive results. Moreover, one sample was invalid from Therascreen FGFR test. Overall, the concordance was very good and reached a kappa value of 0.92. Interestingly, FGFR3 mutations by UroTyper FGFR test were positively associated not only with FGFR3 mRNA overexpression ($r=0.6699$, $p<0.0001$), but also with TROP2 and NECTIN4 ($r=0.5026$ and $r=0.4406$, $p<0.0001$) indicating, that combinations of FGFR targeting with ADC targeting of TROP2 or NECTIN4 could have strong synergistic effects. Hierarchical clustering revealed a homogenous FGFR3 mutated group of tumors simultaneously co-expressing the target genes TROP2, NECTIN4 and PPARG. **Conclusions:** PCR-based FGFR assessment by Therascreen and UroTyper is highly concordant and enables fast, local FGFR assessment within few hours. FGFR3 mutations are associated with increased TROP2 & NECTIN4 expression indicating potential synergistic options which warrants further exploration as part of molecularly stratified clinical trials. Research Sponsor: None.

Describing the genomic landscape of bladder cancer histologic subtypes.

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Background: Histologic subtypes of bladder cancer are associated with poor prognosis and therapy resistance; understanding of their biology can help identify therapies to improve outcomes. We aimed to describe the genomic alteration (GA) landscape of pure urothelial (UC) and histologic subtypes: plasmacytoid (PC), micropapillary (MP), sarcomatoid (SA), small cell/neuroendocrine (SC), squamous cell differentiation (SQ), adenocarcinoma (AD). **Methods:** Approximately 2165 patients (pts) were selected from the Tempus multimodal database. Selection criteria included diagnosis of bladder cancer (UC or histologic subtypes: PC, MP, SA, SC, SQ, AD) and sequencing via the Tempus xT assay. Genomic and immunotherapy biomarkers, including mutations, fusions, copy number variants, tumor mutation burden (TMB-high defined as ≥10 mutations/Mb) and MSI status were determined for each subtype and compared using Fisher's Exact and Kruskal-Wallis tests. **Results:** Among 2165 identified pts, 1738 (80%) had UC (84% pure and 16% mixed histology), Table shows genomic alterations per histologic subtype. Median age at diagnosis was 70. The overall cohort included male (73%), white (84%), and ever smokers (71%). Of 1197 pts with staging information available, 71% tumors were stage IV. TMB-H and MSI-high status were noted in 17% and 1.1% of the overall cohort, respectively, and were relatively similar across histologies. PD-L1 positive status by IHC was noted in 30% in the overall cohort, and statistically lower in PC (7.7%), SC (10%) and AD (8.8%) vs UC (32%), SA (46%) and SQ (45%) ($p<0.001$). Compared to UC, *FGFR3* was significantly lower in SC (9% vs 1%, p=0.003) and AD (9% vs 1%, p=0.001). We noted *FGFR2/3* fusions in 2.6% of the entire cohort and all cases were UC. Compared to UC, *ERBB2* was significantly higher in MP (13% vs 45%, $p<0.001$) and lower in SQ (13% vs 2%, $p<0.001$). *ERBB2* amplification was more common in MP (16%) vs 8% in PC, 6.2% in UC, and 1.6% in SC. **Conclusions:** Distinct genomic alteration patterns were found among different histologic subtypes of bladder cancer and conventional UC. Assessing the genomic landscape of bladder cancer can help identify potential 'actionable' targets and biomarkers, and better inform clinical trial designs. Limitations include lack of clinical data annotation, tumor heterogeneity and retrospective study nature. Research Sponsor: None.

Altered Gene	UC N=1,738 (%)	PC N=25 (%)	MP N=38 (%)	SA N=37 (%)	SC N=113 (%)	SQ N=126 (%)	AD N=88 (%)	p
TERT	1,270 (73)	21 (84)	21 (84)	31 (82)	32 (86)	80 (71)	88 (70)	<0.001
TP53	1,015 (58)	14 (56)	14 (56)	20 (53)	22 (59)	94 (83)	87 (69)	<0.001
RB1	337 (19)	10 (40)	14 (37)	11 (30)	62 (55)	7 (6)	9 (10)	<0.001
ERBB2	220 (13)	6 (24)	17 (45)	4 (11)	9 (8)	3 (2)	7 (8)	<0.001
PIK3CA	276 (16)	3 (12)	4 (11)	13 (35)	22 (19)	49 (39)	5 (6)	<0.001
MTAP	334 (19)	1 (4)	3 (8)	9 (24)	1 (1)	40 (32)	11 (12)	<0.001
BRCA2	50 (2.9)	3 (12)	2 (5.3)	1 (2.7)	2 (1.8)	4 (3.2)	2 (2.3)	0.5
ARID1A	384 (22)	4 (16)	9 (24)	4 (11)	33 (29)	12 (10)	14 (16)	<0.001
FGFR3	158 (9)	2 (8)	4 (11)	7 (19)	1 (1)	13 (10)	1 (1)	0.001

Longitudinal whole exome sequencing of cell-free DNA in advanced bladder cancer.

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Background: The recent approval of agents from novel therapeutic classes including immunotherapy and antibody-drug conjugates has transformed the treatment landscape of advanced bladder cancer. However, even among patients with initially favorable responses to therapy, a subset of patients develop acquired resistance for reasons that are yet to be fully elucidated. **Methods:** To gain insight into the dynamics of tumor evolution during the course of treatment, we performed longitudinal profiling of plasma cell-free DNA in a cohort of 71 patients with muscle-invasive or advanced disease before, during, and/or after specific lines of therapy. To further resolve evolutionary dynamics during the course of treatment, we additionally performed Whole Exome Sequencing (WES) on 47 plasma samples across 25 patients. **Results:** We observed a median tumor purity of 3.8% in the plasma with a range from undetectable (N = 24 samples out of 217 total) to 61%, with tumor purity generally increasing in patients with progressing disease as compared to stable ($p = 0.037$) or to responding disease ($p = 0.002$), consistent with the notion that tumor DNA content in the circulation may act as a proxy for overall tumor burden. Phylogenetic reconstruction in 14 patients using WES data identified growing subclones with potential resistance drivers including *TP53*, *PTEN*, and *FAM46C*. In addition, we identified two cases in which growing subclones showed few shared mutations with regressing clones, demonstrating instead largely distinct somatic mutation profiles. **Conclusions:** Longitudinal WES of cfDNA is feasible in a subset of advanced bladder cancer patients with sufficiently high tumor purity in the blood. In addition, based on our findings of substantial variation in somatic mutations within two reconstructed patient phylogenies, we hypothesize that acquired resistance could in some cases be enabled by marked transitions in the neoantigen repertoire. Research Sponsor: None.

Clinical and molecular characterization of urothelial (UC) vs. small cell carcinoma (SCC) of the urinary tract.

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Background: SCC is an uncommon variant of bladder cancer with sparse data pertaining to its genomic landscape. Utilizing Tempus Lens, a real world clinical and genomic dataset, we investigated the clinical and genomic characteristics of SCC compared to UC. **Methods:** The de-identified Tempus Lens dataset was queried for patients diagnosed with UC or SCC of the bladder or ureter, of any stage. Baseline demographic, pathologic features, and results from blood or tissue-based genomic sequencing were catalogued. Clinical and pathological variables were summarized using descriptive statistics to compare the UC and SCC groups, using a Chi-square or Fisher's exact test for a significance threshold of $P<0.05$. The prevalence of genomic alterations in the two groups were compared using a two proportions Z-test with a significance level of 0.00167, calculated using the Bonferroni correction for multiple comparisons. **Results:** A total of 4,569 pts (UC: 4429; SCC: 140) were included in the analysis. Gender, race, the proportion of patients ≥65 years, stage, and tumor grade were similar between the two groups. Use of blood based genomic sequencing was relatively similar (29.8% and 27.1%) between UC and SCC patients, respectively. Compared to UC, the SCC cohort had a significantly higher prevalence of *TP53* (93.6% vs 60.8%; $P<0.001$), *RB1* (73.6% vs 21.5%; $P<0.001$), and *PTEN* (13.6% vs 5.1%; $P<0.001$) alterations, and a lower frequency of *CDKN2A* (7.1% vs 29.5%; $P<0.001$), *MTAP* (2.9% vs 18%; $P <0.001$) and *FGFR3* (6.4% vs 15.6%; $P=0.003$) mutations. Actionable alterations in SCC cohort included *PIK3CA* (21.4%), *ERBB2* (13.6%), *ATR* (13.6%), *ATM* (9.3%), *BRCA2* (8.6%), *MSH6* (5.7%), *TSC1/2* (4.9%), and *PMS2* (4.3%). **Conclusions:** This is the largest study characterizing the genomic features of SCC. Our findings are consistent with prior studies suggesting a distinct genomic profile of SCC, with actionable alterations in a significant subset of patients. The impact of these alterations on outcomes and therapeutic strategies targeting these mutations warrant further investigation. Research Sponsor: None.

Identification and characterization of prognostic isoforms associated with bladder cancer outcomes.

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Background: Alternative splicing events can represent driver aberrations in cancer the same way as mutations, copy number changes, and gene fusions. We previously identified TP63 isoforms that were associated with prognosis in patients with bladder cancer and other tumor types. However, little is known about how isoform expression heterogeneity in other genes contributes to outcomes in bladder cancer. We hypothesized that expression of alternative isoforms in bladder cancer would be associated with clinical outcomes in a manner distinct from previously seen gene level associations. **Methods:** To examine this, we developed a high-throughput approach to identify and characterize prognostic gene isoforms that are associated with worse prognosis using RNA-sequencing data from The Cancer Genome Atlas (TCGA) bladder cancer cohort (BLCA). To identify gene isoforms that associate with bladder cancer outcomes, we aligned patient reads using HISAT2 and quantified expression for 69,272 isoforms using the Refseq isoform definitions from NCBI and the Stringtie algorithm. We filtered our quantifications to isoforms that belong to a gene with two or more isoforms, and those that had >0.1 Log2 TPM expression. The remaining 42,798 isoforms were tested for association with overall survival using cox regression and based on the following criteria: an isoform had to have a Hazard Ratio greater than 1 with a p-value < 0.05, an FDR adjusted p-value < 0.2 for a log-rank survival statistic using 3 quantile expression thresholds (25, 50 and 75^{th}), and no significant gene-level association with disease prognosis. We validated our quantifications by confirming read coverage at the unique splice junctions for each isoform and by RT-PCR. We then performed differential expression and pathway enrichment analyses for tumors with or without expression of each pathogenic isoform. **Results:** 34 individual isoforms (from 30 genes) fit the criteria for association with survival. Several isoforms identified by our screen, such as FLNB, AXL, and COL6A3 isoforms, were previously shown to be associated with cancer outcomes in other tumor types. Expression of 7 isoforms were confirmed in human bladder cancer (2 isoforms of COL6A1, APLP2, TIAL1, and 1 isoform of FLNB) using RT-PCR. Expression of 21 of these prognostic isoforms were enriched in the aggressive basal squamous molecular subtype. Pathway analysis of TCGA BLCA tumors expressing these isoforms revealed enrichment of gene pathways associated with invasive cancer phenotypes, such as epithelial to mesenchymal transition and MYC targets. **Conclusions:** Specific isoforms are significantly associated with bladder cancer patient survival and suggest that splicing events in certain genes may act as driver aberrations in bladder cancer. Further work will need to be done to establish the regulatory mechanisms as well as how these isoforms contribute to cancer progression. Research Sponsor: NIH; Damon Runyon.

Peripheral biomarker analysis in patients with advanced urothelial carcinoma (UC) after platinum chemotherapy treated with cabozantinib (CABO) plus durvalumab (DURVA): Preliminary analysis from the phase 2 ARCADIA trial.

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Background: Preliminary results of the interim analysis of the ARCADIA trial have shown that combining multitargeted receptor tyrosine kinase inhibitor CABO with the checkpoint inhibitor DURVA has promising activity and a manageable safety profile in patients (pts) affected by UC recurred or progressed after failure of at least one line of platinum-based chemotherapy for metastatic disease in a phase II study (NCT03824691). To identify peripheral blood biomarkers potentially associated with clinical response, we carried out a quantitative profiling of innate and adaptive immune subsets from a subset of treated pts. **Methods:** From 09/2019 and 08/2023 blood samples from 65 pts were collected at baseline and before the third treatment cycle. Absolute cell counts for 29 innate and adaptive immune subsets were determined by multi-parametric flow cytometry. **Results:** In pre-therapy samples a significant higher counts for all CD45+ leukocytes were found in non-responders compared to responders (p=0.0053, Mann Whitney test, n= 27 patients). This was, explained by higher counts for CD16+CD15+ neutrophils (p=0.0005), classical CD14+CD16- (p=0.0119) and CD14++CD16+ intermediate (p=0.0186) monocytes, CD56dim CD16+ NK cells (p=0.0365) and Lin-HLA-DR-/LoCD33+CD14+CD15- M-MDSCs (p=0.0281). At baseline, higher neutrophils counts were associated with worse PFS (p=0.0117, log rank test), while higher eosinophils counts were associated with improved PFS (p=0.0158). Compared to responders, non-responders underwent a significant reduction in post-treatment counts for all CD45+ leukocytes (p=0,0024, Wilcoxon matched pair test), due to reduction of neutrophils (p=0.0068), CD15+CD16- eosinophils (p=0.0068), CD3+ T cells (p=0.0425) CD19+ B cells (p=0.0068), classical monocytes (p=0.0034), activated (HLA-DR+) CD56dim CD16- NK cells (p=0.0068), M-MDSCs (p=0.0161), Lin- HLA-DR-/Lo CD33+ CD14- CD15+ PMN-MDSCs (p=0.001), Lin- HLA-DR+ CD33- pDCs (p=0.0269) and Lin- HLA-DR+ CD33+ mDCs (p=0.0005). **Conclusions:** These preliminary findings suggest that high baseline counts for granulocytes, monocytes and MDSCs may negatively impact on response in pts treated with CABO+DURVA. Moreover, baseline neutrophils and eosinophils counts show opposite impact on PFS. Grant support: NET-2016-02361632 from Italian Health Ministry to A. Anichini. Clinical trial information: NCT03824691. Research Sponsor: None.

Clinicogenomic characterization of patients with rapid tumor progression versus sustained response to frontline systemic therapy for metastatic urothelial carcinoma (mUC).

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Background: mUC often carries a poor prognosis, and a subset of patients (pts) progresses within weeks of starting frontline therapy. While clinicopathologic predictors such as the Bellmunt score have been proposed, predicting this high-risk subset is challenging. Next generation sequencing (NGS) may identify predictive biomarkers for pts with rapid tumor progression, but the predictive value of variant allele frequency (VAF) of genomic alterations is uncertain. **Methods:** An IRB-approved, HIPAA-compliant single institution retrospective database of pts diagnosed with mUC from 1/2013-3/2023 with somatic NGS and were treated with standard of care therapy was generated. Baseline demographics, clinicopathologic features, and NGS results including pathogenic/likely pathogenic mutations, fusions, copy number alterations, and VAF were extracted from the electronic health record. Progression-free survival (PFS) was calculated from the start of frontline (1L) treatment until radiographic/pathologic progression or death from cancer, whichever came first. PFS <120 days was considered rapid progression (RP), and PFS >180 days was considered sustained response (SR). Statistical analysis included chi-square and student paired t-test. **Results:** 260 pts with mUC were identified, and 86 pts had available NGS data. Clinical data cutoff was 9/2023. NGS results used in this analysis were based on the primary tumor (64.0%), distant metastasis (27.9%), or blood (5.8%). Comparing the RP cohort (n=29) vs SR cohort (n=40), there were no significant differences for median age at mUC onset (68 v 68 yrs), proportion of female pts (34 v 28%), Black ancestry (14 v 5%), or smoking history (66 v 68%). Notable variant histologies included squamous cell (28 v 10%, p=0.051) and small cell (0 v 10%, p=NA). 1L treatment involved cisplatin (38 v 43%), carboplatin (17 v 35%), oxaliplatin (0 v 2.5%), or immune checkpoint inhibitor monotherapy (45 v 20%). At mUC, RP cohort pts had more liver metastases (31 v 10%, p=0.027). Median TMB was 10.5 (n=17) vs 6.6 mut/Mb (n=27). No significant difference between RP and SR was observed in the incidence of alterations in *TP53* (52 v 58%), *TERT* promoter (50 v 71%), *PIK3CA* (41 v 28%), *ARID1A* (27 v 23%), and *KMT2D* (14 v 26%). Pts in the RP cohort were significantly more likely to have lower VAF for *TP53* (p=0.006) and *KMT2D* (p=0.028). Amongst 1L platinum-treated pts, low *TP53* VAF remained significantly associated with the RP cohort (p=0.010) and *KMT2D* VAF nearly significant (p=0.077). **Conclusions:** Pts with mUC who rapidly progressed on frontline therapy had a significantly higher liver involvement at mUC diagnosis, a trend toward squamous histology, and a significantly lower VAF for *TP53* and *KMT2D* alterations. VAF is a potential predictive biomarker that should be further investigated. We plan to validate these findings in larger cohorts. Research Sponsor: None.

AI-based morphologic model for prediction of individual patient response to immune checkpoint inhibitors for bladder cancer.

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Background: Immune checkpoint inhibitors (ICI) have been used to treat advanced muscle invasive and/or metastatic bladder cancer. However, ICIs are only effective in 30-40% of cases. In light of potentially significant IRAE's, tools to predict individual patient level benefits are desirable. AI technology offers the opportunity to apply computational methods to predict outcomes from readily available digitized pathology slides. We investigated the utility of an AI platform integrating computational biomarkers based on morphological characterization of digitized H&E slide whole images (WSI) to predict response to ICI. **Methods:** We analyzed H&E-stained whole slide images (WSI) of bladder tumor tissue collected from transurethral resection of bladder tumor (TURBT) from 116 patients with advanced or metastatic bladder cancer at a single institution between 2015-2020. Adjacent multiplex IHC stained specimens were analyzed myeloid and lymphoid marker panels. 20 patients from the overall cohort treated with ICI were designated 'responders' (complete response, partial response, stable disease) and 20 patients were identified as non-responders (progressive disease) based on ICI best clinical/radiographic response. WSIs were divided into small non-overlapping image patches. These image tiles were processed into multiple AI encoder models to extract morphological features. The tile morphological features, represented by high dimensional vectors, were combined by an aggregation model to represent the whole slide morphology and then used to classify the patients into responders vs non-responders to immunotherapy. Area-under-the-receiver operating characteristic (AUC) was used to measure the performance of response prediction. **Results:** Our method shows AUC of 0.708 at classification of the patients (n=40) into responder and non-responder groups. With a cutoff that identifies the top 50% patients (n=20) of high probability of responding to immunotherapy predicted by our models, 75% of them are responders. In the bottom 50% patients (n=20) of the low scores, 75% of them are non-responders. . Multiplex IHC (myeloid and lymphoid panel) was performed using adjacent sections and were characterized yielding deeper mechanistic insight into the inflammatory populations driving predictive morphologic patterns. **Conclusions:** By applying innovative AI morphological analysis on patient WSIs, we generated a computational biomarker that shows promising ability to predict patient response to immunotherapy in bladder cancer. This approach merits future prospective validation and additional patient level analysis in broader cohorts. Research Sponsor: Department of Defense; PathomIQ Inc.

AUC 0.708		Predicted: Responders	Predicted: Non-responders
Ground Truth	Responders	75%	25%
	Non-responders	25%	75%

Liquid biopsy as promising source of plasma extracellular vesicle biomarkers of response to cabozantinib (CABO) plus durvalumab (DURVA) in patients with advanced urothelial carcinoma (UC) or non-UC variant histologies (VH) after platinum chemotherapy: The phase 2 ARCADIA trial.

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Background: As components of the liquid biopsy, Extracellular Vesicles (EVs) have gained major interest as biomarkers of diagnosis, prognosis and prediction of response/resistance to cancer therapies. Here we investigated if plasma EV immune profile, size and concentration in concert with plasma proteomics might discriminate responding from non-responding patients affected by advanced urothelial carcinoma (UC) or non-UC variant histologies (VH) undergoing cabozantinib (CABO) plus Durvalumab (DURVA) combination therapy after platinum chemotherapy (NCT03824691). **Methods:** We evaluated 40 patients for their plasma EV profile at baseline and at the first reassessment after 2-4 months of therapy. Baseline samples of 50 patients (40 plus additional 10 patients) were evaluated for their predictive potential. EVs were profiled using modified MACSplex technology (Miltenyi Biotec) coupled with flow cytometry and nanoparticle tracking analysis (NTA). Whole plasma was also searched for further indicators of response/resistance by proteomics (92 analytes, Immune-oncology panel, Olink). **Results:** Preliminary analysis of the single EV markers measuredin baseline samples evidenced no major association with response, although patients with VH histology showed a significant enrichment of CD1c and CD14 expressing EVs. Upon inclusion in the analysis of the on-therapy time point we were able to detect in the whole case set an increase of immune markers, including CD14, CD1c, CD2, CD20, CD8 and CD69; EV markers CD9, CD63 and CD81; platelet markers CD29, CD31 and CD326. This was also reflected by the global distribution of EV markers, which evidenced unexpectedly high levels of EVs exposing CD81 EV marker and CD8 already at baseline, with a further increase after therapy initiation. Finally, the dichotomization by response highlighted that a statistically significant increase of immune EVs was detectable almost exclusively in responding patients. NTA and plasma proteomics are currently ongoing. **Conclusions:** Our preliminary results suggest that the early dynamics in plasma EVs may inform on the clinical outcome to DURVA plus CABO. The significant increase of EVs expressing immune markers measured at first reassessment in responding patients may derive from the activation of the immune system induced by therapy. The comprehensive analysis of EV profiles, size and concentration together with plasma proteomics could give rise to predictive/prognostic biomarkers of response in this clinical setting, especially in patients with non-UC variant histologies. Acknowledgements. AIRC IG-25078 to VH, NET-2016-02361632 from Italian Health Ministry to A. Anichini. Clinical trial information: NCT03824691. Research Sponsor: None.

Predicting efficacy in patients with locally advanced (LA)/metastatic urothelial carcinoma (mUC) treated with avelumab using machine learning and explainability approaches.

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Background: Internationally avelumab is approved as maintenance therapy for patients (pts) with LA/mUC whose disease did not progress after 1L platinum-based chemotherapy. However, 54% of pts progressed on avelumab. Limited data are available on predictive biomarker of efficacy. Artificial intelligence (AI) methods are being increasingly investigated to generate predictive models applicable in clinical practice. In this study, we developed a set of machine learning (ML) classifiers and survival analysis algorithms using real-world data to predict response and progression free survival (PFS) in LA/mUC patients treated with avelumab. We also applied explainability to the developed algorithms. **Methods:** We prospectively collected real-world data from 115 pts receiving Avelumab from 2021 to 2022 treated in 20 institutions in Italy (MALVA dataset). In order to predict the efficacy of immunotherapy (IO), 2 different outcomes were studied: Objective Response Rate (ORR) and Progression Free Survival (PFS). The dataset was split between training and test set, with a 80%-20% ratio.The missing values were imputed using a Bayesian Ridge iterative imputer, fitted on the training set. Eight different classifier models were used for ORR: XGBoost (XGB), Logistic Regression (LR), Random Forest (RF), Multilayer Perceptron (MLP), Support Vector Machine (SVM), Adaboost (AB), Extra Trees (ET) and LightGBM (LGBM). Five ML survival analysis models were used to analyse PFS: Cox Proportional Hazards (CPH), Random Survival Forest (RSF), Gradient Boosting (GB), Extra Survival Trees (EST) and Survival Support Vector Machine (SSVM). Finally, SHAP values, an eXplainable AI (XAI) technique, were calculated to evaluate each feature and to explain the predictions. **Results:** According to clinical expertise, 31 features were selected through a clinical hypothesis. For ORR prediction, the two best performing models were XGB and ET, both without using oversampling. On the test set, XGB achieved a F1 score of 0.77, accuracy of 0.77 and AUC of 0.81, while ET reached F1 score and accuracy of 0.81 and AUC of 0.80. Regarding the prediction of PFS, EST and RSF obtained the best performances with a c-index of 0.71 and 0.72, and Average AUC of 0.75 and 0.76, respectively. According to SHAP, the most important feature for predicting ORR was: ORR after 1st line CHT, while bone metastases, absolute leukocytes number at baseline and ECOG PS were the most important features for the PFS prediction. **Conclusions:** Machine learning is useful to predict efficacy in advanced urothelial carcinoma. The explainability models confirmed what have been discovered within the last years of immune-research conferring trustworthiness to the ML models. Further validation of these approaches on larger and external pts cohorts is needed. Research Sponsor: None.

689 Poster Session

Dicycloplatin: Assessing the efficacy of a novel platinum analog for treatment of urothelial carcinoma of the bladder.

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Background: Platinum-based chemotherapies are a component of standard-of-care regimens for urothelial carcinoma (UC). These nephrotoxic drugs are often dose-limiting, with cisplatin and carboplatin most used. Dicycloplatin (DCP) has better solubility and stability, with comparable efficacy and better tolerability. Some suggest use of DCP as primary treatment for non-muscle-invasive bladder cancer. We exposed UC cell lines to DCP *in vitro* to assess efficacy. **Methods:** A high grade (IV) *in vitro* UC cell line (TCCSUP) was exposed to varying concentrations of cisplatin (0-600 ug/mL), carboplatin (0-600 ug/mL), oxaliplatin (0-4.0 ug/mL), and DCP (0-350 ug/mL). Grade II-IV cells were exposed to concentrations of DCP (0-350 ug/mL) to assess time- and concentration-dependence of growth inhibition, and intravesical simulation. Growth inhibition was determined following exposures of 24, 48, and 72 hours using exposure to a tetrazolium dye assessing mitochondrial dehydrogenase activity. **Results:** DCP, cisplatin, and carboplatin effectively achieved >90% cell-kill at 72 hours. Concentrations of 325 ug/mL DCP, 50 ug/mL cisplatin, and 600 ug/mL carboplatin are sufficient for >90% cell-kill, with cisplatin boasting highest kills at lowest concentration/time intervals. Dose- and time-dependent cell-kill were demonstrated at varying concentrations of DCP in grade II-IV cell lines, including cells exposed in a intravesical fashion. **Conclusions:** DCP has *in vitro* cell-kill efficacy in a time- and concentration-dependent manner in grade II-IV UC cell lines, showing promise for its IV, PO, and intravesical use for UC of the bladder in the primary and adjuvant/neoadjuvant setting. Animal studies are forthcoming to assess *in vivo* efficacy prior to proceeding with clinical trials. Research Sponsor: None.

Mechanisms and strategies to overcome resistance to enfortumab vedotin in bladder cancer.

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Background: Enfortumab vedotin (EV) is an antibody-drug conjugate (ADC) targeting NECTIN4, a surface protein highly expressed in bladder tumors, and is currently approved for metastatic urothelial carcinoma (mUC). Based on its demonstrated benefit, EV is currently being evaluated in earlier UC settings, including non-muscle invasive bladder cancer (NMIBC). Because ADCs are associated with primary or secondary resistance, it is crucial to understand mechanisms of EV resistance. We sought to develop a preclinical bladder cancer model of EV resistance with which we could investigate mechanisms of and strategies to overcome resistance. **Methods:** The RT112 bladder cancer cell line, which expresses high levels of NECTIN4, was used to develop a model of resistance. RT112 cells underwent "cycles" of treatment with 5-7 days EV with subsequent recovery and passaging of surviving cells. Each "cycle" used escalating doses of EV. Parental RT112 cells were cultured in parallel. Cell lines were profiled with flow cytometry, western blotting, and bulk RNA sequencing. Second-generation chimeric antigen receptor (CAR) T-cells were engineered with a single chain fragment variable (scFv) designed with the variable regions of the heavy (VH) and light chains (VL) of enfortumab, the human monoclonal antibody specific for NECTIN4. Drug dose-response and CAR T-cell killing assays were performed with RT112 parental and EV-exposed cells. After 24h, drug or CAR T-cells were added at indicated concentrations or effector-to-target (E:T) ratios, and cell count and growth monitored using an IncuCyte S3. **Results:** RT112 cells undergoing treatment "cycles" with escalating concentrations of EV starting at 0.5 μg/ml and culminating at 30 μg/ml yielded a generation of cells that exhibited a 4-5-fold increase in IC50 for EV. The "EV-resistant" RT112 cells had comparable NECTIN4 levels and TROP2 levels compared to parental cells. Preliminary results suggest upregulation of P-glycoprotein and TGF-β genes in resistant cells. The EV resistant cells were less sensitive to MMAE, the payload of EV. EV-resistant RT112 cells were more sensitive to sacituzumab govitecan (SG), a Trop-2-directed antibody conjugated to the topoisomerase inhibitor SN-38. The EV-resistant RT112 cells were equally susceptible to killing by NECTIN4-directed CAR T cells compared to parental RT112 cells. **Conclusions:** In conclusion, we developed a preclinical *in vitro* model of bladder cancer resistant to EV. Resistance to EV was largely due to resistance to the payload MMAE, and not due to downregulation of the surface target NECTIN4. The EV resistant bladder cancer cells remained sensitive to NECTIN4-directed CAR T cells, suggesting 1) NECTIN4 remains a relevant target even after cells develop EV resistance, and 2) non-overlapping mechanisms of resistance to ADCs versus CAR T therapy. Finally, treatment using SG represents an alternative strategy after EV resistance. Research Sponsor: UCSF School of Medicine Dean's Yearlong Fellowship.

Correlation of artificial intelligence (AI)-based spatial characteristics of tumor-infiltrating lymphocytes outcomes with immune checkpoint inhibitors (ICIs) in patients (pts) with metastatic urothelial cancer (mUC).

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Background: Quantification of tumor-infiltrating lymphocytes (TILs) in archival hematoxylin and eosin (H&E) specimens of muscle-invasive urothelial cancer (MIUC) specimens can help assess tumor microenvironment (TME) and serve as prognostic and predictive biomarkers to assess outcomes with ICI. There is an unmet need to develop non-invasive computational pathology-based models based on the spatial characteristics of TILs on H&E tissue images for predicting outcomes with ICI in pts with mUC. **Methods:** We retrospectively analyzed 335 adult pts with mUC treated with ≥2 cycles of ICI with atezolizumab (A) or pembrolizumab (P) at Cleveland Clinic between 2015 and 2023. We used this cohort to validate a prognostic model for bladder cancer (BC) originally trained on the Cancer Genome Atlas (TCGA) dataset. Of the 335 pts in this cohort, we had archival H&E slides from biopsy or radical surgery available for 56 pts (S_1). We developed a tumor segmentation model by leveraging the U-net deep learning network. Within the segmented regions, nuclei were segmented and classified into TILs and non-TILs using the HoVer-Net algorithm. Spatial graphs involving the TILs as the nodes of the graphs were constructed and a total of 350 spatial statistics relating to the distances between the TILs and non-TILs were extracted. Using the least absolute shrinkage and selection operator (LASSO) model, the 14 most prognostic features were identified using tissue images from a total of 361 patients with MIBC from the Cancer Genome Atlas (TCGA) (S_2). These features were utilized to develop a Cox regression model, aiming to assess the risk of death for individual patients from the S_2. The Cox model was then applied to predict risk and outcome for patients from S_1. **Results:** In S2, high-risk patients, as identified by the AI model, had a median overall survival (OS) of 16 months, while low-risk patients had a median OS of 21 months. The model's performance was validated using a blinded dataset from S1, and it showed significant prognostic value for OS in S1 patients, with Hazard Ratio (HR)=1.61 (95% Confidence Interval (CI) =1.18-2.2, and p-value=0.0013). The median OS for the high-risk group based on our model was 26 months and 39 months for the low-risk group, HR 1.90 (95% CI = 0.97-3.73, p-value = 0.036). **Conclusions:** Computational image features related to spatial architectural patterns of TILs and non-TILs on H&E tissue images correlated with OS in pts with mUC receiving ICI in our real-world cohort. Additional independent multi-site and prospective validation of these findings are warranted. Research Sponsor: None.

EIF2S1 as a novel diagnostic marker for bladder cancer in urinary extracellular vesicles.

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Background: Urinary extracellular vesicles (uEVs) secreted directly from BCa are considered a promising tool for diagnosing BCa, as they contain cancer-specific molecules. Among them, proteins in uEVs have attracted considerable attention, and several membrane EV proteins have been reported as urinary markers for BCa. However, few studies have focused on non-membranous (cytoplasmic) EV proteins. This study aimed to explore and validate a uEV-based diagnostic marker for BCa, focusing on cytoplasmic EV proteins. In addition, the functions of the identified protein were assessed. **Methods:** uEVs were isolated by ultracentrifugation with a sucrose cushion. Shotgun proteomics (TMT-labeled LC-MS/MS) was performed on uEVs from seven patients with BCa and four healthy individuals. Diagnostic marker candidates were selected from the identified cytoplasmic EV proteins and validated with targeted proteomics (SRM/MRM) of uEVs from 49 patients with BCa and 48 individuals without BCa, including patients with hematuria. The functional analysis of the identified EV protein was conducted in vitro. **Results:** Shotgun proteomics identified 1960 proteins, of which 17 cytoplasmic EV proteins were significantly elevated in the uEVs from patients with BCa (Fold change >1.5, p-value < 0.05). Of these, all ten measurable EV proteins were confirmed to be significantly elevated in urine from patients with BCa, of which EV-EIF2S1 showed the best diagnostic performance (ROCAUC: 0.83, sensitivity: 80%, specificity: 77%) in the validation cohort. Additionally, EV-EIF2S1 distinguished patients with BCa from non-BCa hematuria patients in a suitable manner (ROCAUC: 0.92, sensitivity: 82%, specificity: 83%). In the functional analysis of EIF2S1 in BCa cell lines T24 and 5637, the knockdown of EIF2S1 markedly inhibited cell proliferation. Cell cycle studies showed that the knockdown of EIF2S1 resulted in cell cycle arrest and induction of apoptosis. Therefore, EIF2S1 was considered an essential protein for the growth and survival of BCa cells. **Conclusions:** We identified EIF2S1 in uEVs as a novel diagnostic marker for BCa, enabling accurate and non-invasive diagnosis for BCa in a hematuria setting. Research Sponsor: Japan Society For The Promotin of Science.

ABC transporter expression to predict therapeutic effect of enfortumab vedotin in urothelial cancer.

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Background: Enfortumab vedotin (EV) is an antibody-drug conjugate consisting of anti-Nectin-4 antibody and is approved for metastatic urothelial cancer. Predictors of therapeutic benefit of EV have not been established since nectin-4 expression varies widely with the course of treatment. ATP Binding Cassette (ABC) transporters which export the administered anti-cancer drugs out of the cells have been postulated as one of the mechanisms of therapeutic resistance to EV. In this study, we evaluated the expression of Nectin-4 and ABC transporters in primary biopsy tissues, primary radical resection tissues, and metastatic sites from urothelial cancer patients and evaluated their association with prognosis after EV therapy. **Methods:** We studied 16 patients who received enfortumab vedotin for metastatic urothelial cancer. Biopsy of primary tissue, radical surgery of primary tumor, and resection of metastatic sites was performed in 16, 7, and 4 patients, respectively. In these specimens, the expression of nectin-4 and ABC transporters was evaluated by immunostaining. Among ABC transporters, we evaluated MDR1 (ABCB1), MRP1 (ABCC1), and BCRP (ABCG2) since they have been reported to be associated with anticancer drug resistance. Staining intensity on the cell membrane was classified into 0 to 3 according to the evaluation criteria of HER2. We investigated the relationship between the expression of nectin-4 and ABC transporters and survival after EV therapy. **Results:** Nectin-4 was positive in all patients (score 3 in 12 patients, score 1 in 4 patients) in primary biopsy. All patients tested negative for MDR1. MRP1 was positive in 11 (score 2 in 2 patients and score 1 in 9 patients), and BCRP was positive in 14 (score 2 in 10 patients, score 1 in 4 patients). Nectin-4 expression decreased in radical surgery tissues and metastatic sites. On the other hand, ABC transporter expression remained unchanged or rather increased in radical surgery tissues and metastatic sites (Table). Patients with both MRP1 and BCRP expression in the primary biopsy specimen (n=8) had significantly worse PFS and OS after EV therapy while nectin-4 expression in the primary biopsy specimen was not associated with survival. **Conclusions:** Patients with ABC transporter expression had a poor prognosis after EV therapy, although nectin-4 expression in primary biopsies was not associated with prognosis. Nectin-4 expression tended to decrease, while the ABC transporter remained unchanged or enhanced as the disease progressed. Research Sponsor: None.

	Primary Biopsy Tissues (n=16)		Radical Resection Tissues (n=7)		Metastatic Sites (n=4)	
	Score	n (%)	Score	n (%)	Score	n (%)
Nectin-4	3	12 (75%)	3	2 (29%)	3	1 (25%)
	1	4 (25%)	2	3 (42%)	1	1 (25%)
			1	2 (29%)	0	2 (50%)
MDR1	0	16 (100%)	0	7 (100%)	3	1 (25%)
					1	3 (75%)
MRP1	2	2 (13%)	2	1 (14%)	3	1 (25%)
	1	9 (56%)	1	3 (43%)	1	3 (75%)
	0	5 (31%)	0	3 (43%)		
BCRP	2	4 (25%)	2	1 (14%)	2	1 (25%)
	1	10 (63%)	1	6 (86%)	1	3 (75%)
	0	2 (13%)				

Variant subtypes in bladder cancer and CA125-positive cancer cell state.

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Background: Variant subtypes in bladder cancer are clinically aggressive tumors associated with poor prognosis. The rarity of these tumors has made molecular characterization elusive. The aim of this study was to identify cell states unique to variant subtypes using single cell RNA sequencing. **Methods:** Fresh tissue was collected from bladder cancer patients undergoing surgery at our institution and sequenced using a bead-based single-cell RNA sequencing platform (SEQWELL). Tissue from histologic variants and high grade pure urothelial tumors were analyzed together for comparison. Pathologic diagnoses were independently confirmed. Analysis was performed using Seurat. Immunostaining validation was performed on a separately banked cohort. Bulk RNA sequencing data and clinical data were extracted and analyzed from The Cancer Genome Atlas (TCGA) database. **Results:** We generated a single cell RNA sequencing atlas of 9 variants (micropapillary, nested, squamous differentiation, pleomorphic giant-cell like, plasmacytoid, small cell) with 3 pure urothelial tumors for comparison. Our analyses reveal a tumor cell state shared among multiple variants that is characterized by highly specific expression of *MUC16* (CA125), *KRT24*, and *WISP2* (Fig. 1). This cell state has transcriptional hallmarks of epithelial-mesenchymal transition and luminal-basal plasticity, and its signature is associated with poor survival and resistance to chemotherapy. Immunohistochemistry in a validation cohort demonstrates that CA125+ cells are found only in tumors with variant histology and not in conventional high-grade and low-grade urothelial carcinomas. Within variants tumors, CA125+ cells are more enriched in metastatic sites compared to the primary tumors, consistent with a more aggressive phenotype. **Conclusions:** A CA125+ cell state in variant subtypes in bladder cancer is associated with aggressive molecular features. Further investigation of this cell state is needed to define its role in the pathogenesis of variant tumors.
Research Sponsor: California Urology Foundation.

Development and validation of a novel prognostic model for disease-specific survival in patients with non-metastatic small cell carcinoma of the bladder.

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Background: Small cell carcinoma of the bladder (SCCB) is a rare variant of bladder cancer with limited data informing prognosis. We present a novel prognostic model for disease specific survival (DSS) for patients with non-metastatic (M0) SCCB, derived from the Surveillance, Epidemiology and End Results (SEER) database. **Methods:** The SEER database (18 registries/ November 2020) was queried with the ICD-10 topography codes C67.0-C67.9 (bladder), and the morphologic code 8041 (SCCB). Eligible patients (adults, histologic confirmation, available follow-up/staging data, M0) were randomly divided into a training (TC) and a validation cohort (VC) (7:3 ratio). Variables significantly associated with DSS were identified with multivariate Cox regression and backwards stepwise conditional approach and inserted in the model. Points were assigned to each variable based on the formula: *Probability of an event at time* $t=S_o(t)^{\exp(\beta x)}$, (β = regression coefficients, x = observed covariate values, S0(t) = survival function). Cumulative risk points were assigned to each patient and three distinct risk categories for DSS were constructed. Harrel's C-statistic with bootstrap resampling was used for internal (TC) and external (VC) validation. Model performance was compared to the AJCC 8th edition (likelihood ratio test -LRT). **Results:** A total of 1039 patients were included (739 TC, 300 VC). No statistically significant differences in baseline characteristics/survival outcomes were identified between TC and VC. Age (years), T/N stage, radical cystectomy, chemotherapy, and radiation were significant variables inserted in the multivariate model (table). Patients were stratified to three risk groups (low, intermediate, high) based on the total cumulative risk points collected. Median DSS was NR (95%CI; NR, NR), 25 (95% CI; 18-32) and 9 months (95% CI; 7-11) for the low, intermediate, and high-risk category, log-rank p<.001. Harrel's C-statistic for the model was 0.70 (95%CI;0.67-0.73) in the TC and 0.66 (95%CI; 0.61-0.71) in the VC. In comparison, C-statistic for the AJCC 8th edition was 0.56 (95% CI; 0.52-0.59) and 0.53 (95% CI; 0.51 to 0.57), respectively. The LRT demonstrated superior performance of the model compared to AJCC (p<.001). **Conclusions:** We present a novel prognostic model for DSS in patients with locoregional SCCB composed of variables readily available in daily practice, which may serve as a useful tool for individualized risk assessment of patients with this rare malignancy. Further validation in prospective studies/clinical trials is warranted. Research Sponsor: None.

Variables		DSS Points	Variables		DSS Points
1.Age Group	*<75y*	0	*4.Radical Cystectomy*	*Yes/No*	0/43
	75-84y	17	*5.Chemotherapy*	*Yes/No*	0/42
	85+y	48	*6.Radiation*	*Yes/No*	0/33
2.T Stage	*T1/T2*	0/46	***Categories***	*Low*	<100
	T3/T4	66/100		*Intermediate*	100-170
3.N Stage	N0/N1/N2+	0/39/57		*High*	171+

Platinum eligibility (PE) criteria for patients with metastatic urothelial carcinoma (mUC): Results of a physician survey in 5 European countries.

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Background: The standard of care for mUC is platinum-based chemotherapy (PBC) followed by avelumab first-line (1L) maintenance in patients without disease progression. Guidelines for mUC recommend 1L treatment based on eligibility for PBC (cisplatin or carboplatin), but the definition of PE remains unclear, and little is known about criteria used by European physicians to define PE in clinical practice. In this cross-sectional study, we assessed treatment decision-making factors and clinical thresholds used by European physicians determine PE and examined their alignment with published US physician thresholds. **Methods:** Physicians from France, Germany, Italy, Spain, and the UK completed a quantitative online survey in Aug/Sep 2022. We adapted Gupta et al's ASCO-GU 2019 and ASCO 2022 US-based surveys, which identified thresholds for clinical criteria used by US physicians to define PE. This EU survey included clinical parameters with different age and creatinine clearance (CrCl) thresholds, plus Eastern Cooperative Oncology Group performance status (ECOG PS) and other relevant criteria. Participants reported the percentage of patients they perceived were platinum eligible and ranked criteria to determine PE. All analyses used descriptive statistics. **Results:** 503 physicians (69% oncologists, 31% urologists) completed the quota-based survey. Most had been in practice for >10 years (69%), treated 5-19 patients with mUC per month (58%), and practiced in a public teaching hospital (40%). Most patients who received 1L systemic treatment were PE (77%), ranging from 75% in Italy to 79% in Spain. Most respondents chose >80 years (33.2%) or >75 years (24.1%) as the age threshold for platinum ineligibility. Age thresholds selected were significantly different across countries, years of practice, and practice settings ($p<0.001$). Responses for ECOG PS and peripheral neuropathy thresholds for platinum ineligibility were evenly split between ECOG PS ≥2 (40.6%) and ≥3 (45.3%) and between grade ≥2 (44.3%) and ≥3 (41.7%) peripheral neuropathy. The most frequent responses are summarized (Table). **Conclusions:** Physicians in Europe considered most patients with mUC to be platinum eligible. Criteria to determine PE were broadly consistent with previous US-based studies, except for age. The low age threshold observed is at odds with the older age of the mUC patient population. Wider use of these criteria could support clinical decision-making, reduce variations in care, and improve patient outcomes. Research Sponsor: The study was sponsored by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945) and was previously conducted under an alliance between the healthcare business of Merck KGaA, Darmstadt, Germany and Pfizer.

Criteria	Threshold	Responses, % (N=503)
Age, years	>75	24.1
	>80	33.2
ECOG PS	≥2	40.6
	≥3	45.3
CrCl, mL/min	<25	28.6
	<30	34.8
Peripheral neuropathy grade	≥2	44.3
	≥3	41.7
New York Heart Association heart failure class	II	24.5
	III	58.4
CrCl for patient with ECOG PS 2, mL/min	<40	22.7
	<30	32.2
CrCl for cisplatin ineligibility, mL/min	<40	22.3
	<50	34.4

CrCl, creatinine clearance.

Avelumab first-line maintenance therapy for locally advanced/metastatic urothelial carcinoma: Results from the real-world US PATRIOT-II study.

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Background: In the JAVELIN Bladder 100 phase 3 trial, avelumab first-line maintenance (AVE 1LM) + best supportive care (BSC) improved overall survival (OS) and progression-free survival (PFS) vs BSC alone in patients (pts) with locally advanced/metastatic urothelial carcinoma (la/mUC) with no disease progression following 4-6 cycles of platinum-based chemotherapy (PBC). PATRIOT-II aimed to describe real-world outcomes in pts with la/mUC treated with AVE 1LM who were progression-free after 1L PBC. We hypothesized that outcomes would be similar to those of JAVELIN Bladder 100. **Methods:** PATRIOT-II is an observational, retrospective study in US pts with la/mUC treated in geographically dispersed community and academic centers. Pts receiving AVE 1LM were eligible. Data were collected via medical records for a minimum of 52 weeks (wks) from AVE 1LM initiation. This analysis focuses on ≥24 wks post AVE 1LM initiation. Survival and safety outcomes were assessed; analyses are descriptive in nature. **Results:** 160 pts from 37 sites, a mix of oncology practices and community/academic centers, were included with median age, 70 (range, 40-90) years; 123 (77%) male; 118 (74%) White, non-Hispanic; 77 (49%) lower tract and 49 (31%) upper tract tumors; 119 (74%) ECOG PS 0/1; 70 (44%) and 51 (32%) known visceral (excluding bone) or non-visceral metastases (mets), respectively; 31 (19%) liver mets; and 64 (40%) creatinine clearance >60 mL/min. 100 (62.5%) and 60 (37.5%) pts had received 1L cisplatin or carboplatin, respectively. 130 pts (objective response rate, 81% [complete response, 21; partial response, 109]) had an investigator-assessed response to 1L PBC. Pts initiated AVE 1LM at a median of 4 wks (IQR, 3-6) after PBC completion. At data cutoff, 120 pts (75%) had discontinued AVE 1LM, 89 (74% of 120) due to progression/adverse events (AEs)/other non-death related reasons. Median time on AVE 1LM was 4.1 months (mo) (IQR, 2.3-8.7); median follow-up time post AVE 1LM initiation was 11.5 mo (IQR, 7.5-16.3). Table shows OS and PFS data. Most common documented treatment-related AEs (any grade) included hypothyroidism (n=7 [4%]), anemia (n=6 [4%]), blood creatinine increased (n=6 [4%]), fatigue (n=6 [4%]), and nausea (n=6 [4%]). Grade 3+ AEs occurred in 19 (12%), with no Grade 5 AEs. No new safety signals were noted. **Conclusions:** Results complement JAVELIN Bladder 100 and align with other AVE 1LM real-world studies. Limitations include retrospective data, lack of randomization and central scan review, missing data, selection bias, and confounders. PATRIOT-II further supports the level I evidence for AVE 1LM as standard of care in la/mUC not progressing on 1L PBC. Research Sponsor: This study was sponsored by EMD Serono (CrossRefFunder ID: 10.13039/100004755) and was previously conducted under an alliance between the healthcare business of Merck KGaA, Darmstadt, Germany and Pfizer.

Survival Outcomes at ≥24 wks Post AVE 1LM Initiation	Median (95%CI), mo
OS from start of AVE 1LM	20.3 (15.6-25.0)
OS from start of 1L PBC	26.9 (24.1-29.7)
Investigator-assessed PFS from start of AVE 1LM	6.6 (3.8-9.3)

Oncologic outcomes of neoadjuvant chemotherapy and lymph node dissection with partial cystectomy for muscle-invasive bladder cancer.

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Background: Partial cystectomy (PC) offers potential benefits for select patients with muscle-invasive bladder cancer (MIBC). However, the oncologic efficacy of PC may be compromised due to the underutilization of standard-of-care modalities, such as neoadjuvant chemotherapy (NAC) and pelvic lymphadenectomy (PLND). We aimed to assess factors influencing the incorporation of NAC and PLND with PC and evaluate their impact on overall survival (OS). **Methods:** We identified patients with cT2-4N0M0 BCa who underwent PC between 2004 and 2019 using the National Cancer Database (NCDB). The primary endpoint was OS. Kaplan-Meier analysis compared OS between PC patients who did and did not receive NAC. Multivariate Cox Proportional Hazards (CPH) model assessed the impact of age, sex, race, insurance, income, Charlson-Deyo Index (CDI), clinical T-stage, facility type, histology, surgical margins, NAC, PLND adequacy (≥10 LN yield), and adjuvant radiation treatment on OS. Multivariate logistic regressions were performed to examine predictors of NAC and PLND receipt in PC patients. **Results:** Of 2,832 patients included, 231 (8.1%) patients received multi-agent NAC with PC and had improved median OS compared to those who did not (115.0 vs. 87.4 months, $p<0.001$). This finding persisted in the adjusted CPH model, where private insurance, NAC, and PLND significantly improved OS, especially when PLND yielded ≥10LN. Conversely, age >80, CDI >2, cT3-4, positive margins, and adjuvant radiation all increased adjusted mortality risk. After controlling for clinicopathologic variables, females were less likely to receive PLND (OR=0.634, $p<0.001$), while NAC was more likely administered to PC patients diagnosed from 2015-2019 (OR=2.177, p=0.022). PC patients who received NAC were more likely to have PLND performed as part of their treatment regimen (OR=2.189, $p<0.001$). Additionally, patients treated at academic centers were more likely to have NAC administered and PLND performed (OR=1.745, p=0.003; OR=2.465, $p<0.001$, respectively). **Conclusions:** Despite guidelines, there is an insufficient utilization of NAC and PLND when performing PC. Our analysis underscores the significant OS benefit of these recommended treatments as part of MIBC care. Importantly, we highlight a gradual increase in NAC and PLND receipt in recent years, centered largely at academic facilities. Notably, gender disparities exist in PLND receipt, emphasizing the need for further investigation. Research Sponsor: None.

Variable	HR for OS	p-value
Age (Ref: <65)		
65-79	1.029	0.838
80+	1.885	**<0.001**
cT Stage (Ref: cT2)		
cT3	1.358	**0.001**
cT4	2.575	**<0.001**
Insurance (Ref: Uninsured)		
Private	0.515	**0.016**
Chemotherapy (Ref: No NAC)		
NAC	0.657	**0.01**
PLND (Ref: No PLND)		
PLND <10 yield	0.856	0.056
PLND ≥10 yield	0.586	**<0.001**
Radiation (Ref: No Radiation)		
Adjuvant Radiation	1.492	**0.005**

*Model adjusted for clinicodemographic variables.

Population based trends in intravesical gemcitabine use among patients with high-risk non-muscle invasive bladder cancer.

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Background: Intravesical gemcitabine (iGEM) use among patients with high-risk non-muscle invasive bladder cancer (HR NMIBC) has shown effectiveness towards preventing or delaying tumor recurrence, although Bacillus Calmette-Guérin (BCG) remains the standard of care for newly diagnosed HR NMIBC. This retrospective cohort study investigated iGEM users and reported their treatment patterns among SEER-Medicare enrollees newly diagnosed with HR NMIBC patients naïve (BCG-N) or exposed (BCG-Exp) to BCG therapy. **Methods:** Patients enrolled inMedicare Part A & B fee-for-service enrolled, with HR NMIBC, defined by Tis, Ta, T1, N0, M0 and ≥65 years with iGEM use between 2008-2020 were evaluated. Patients with missing TNM stage, low/ intermediate risk NMIBC, or other primary cancers were excluded. Index date was defined as the first claim of iGEM after HR NMIBC diagnosis, regardless of their prior BCG use. Patients were followed until the earliest event of death, end of Medicare advantage enrollment, or data availability end (12/31/2020). Demographic and clinical characteristics were reported in the baseline period (12-month pre-index) and treatment patterns were reported calendar year post-index date for BCG-N and BCG-Exp cohorts. **Results:** The analysis included 277 BCG-N and 402 BCG-Exp patients receiving iGEM. In both cohorts, mean age was >75 years, ≥80% were male, and >90% were White. The mean (SD) national cancer index comorbidity index score was 0.85 (0.7) for BCG-N and 0.63 (0.7) for BCG-Exp. Intravesical therapy use beyond a perioperative instillation during the baseline period was observed in 27% of BCG-N and 14% of BCG-Exp patients; docetaxel (17% BCG-N, <1% BCG-Exp) and mitomycin (12% BCG-N, 14% BCG-Exp) were most common. The median number of iGEM doses in the BCG-N group was 6 (IQR 1,8) with mean (SD) of 28 (43) days of retreatment interval. In BCG-Exp, the median number of iGEM doses was 6 (IQR 2,9) with mean (SD) of 23 (26) days of retreatment interval. The table shows increasing iGEM use in both BCG-N and BCG-Exp groups, with 70% of BCG-N in years 2019 through 2020, and 22-30% of BCG-Exp patients receiving iGEM in years 2017 through 2020. **Conclusions:** Recent BCG shortages may have played a significant role in recent increased uptake of iGEM in both BCG-N and BCG-Exp cohort among HR NMIBC patients. Further information on the efficacy and safety outcomes of iGEM vs BCG in various HR NMIBC populations are needed. Research Sponsor: Janssen Scientific affairs.

iGem use 2008-2020.

Year	BCG-N (n=277)	BCG-Exp (n=402)
2008-2012, n (%)	12 (4.3)	58 (14.4)
2013-2016, n (%)	28 (10.1)	132 (32.9)
2017-2018, n (%)	42 (15.2)	122 (30.3)
2019-2020, n (%)	195 (70.4)	90 (22.4)

Risk factors for neoadjuvant chemotherapy-induced acute kidney injury in patients with muscle-invasive bladder cancer: A multicenter retrospective study.

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Background: Neoadjuvant chemotherapy (NAC)-induced acute kidney injury (AKI) is one of the frequent complications in patients with muscle-invasive bladder cancer (MIBC) and we previously have reported the negative impact of NAC-induced AKI on oncological outcomes. However, its risk factors remain unclear. **Methods:** This multi-institutional retrospective study included 517 patients with MIBC who received 2–4 cycles of NAC followed by radical cystectomy. AKI was defined according to the KDIGO criteria. Patients were divided into two groups: patients who developed any stage AKI during NAC (AKI group) and patients who did not (non-AKI group). Multivariable logistic regression analysis was performed to identify the risk factors for NAC-induced AKI. The predictive abilities for AKI were evaluated using the area under the receiver operating characteristic curve. **Results:** The median age was 69 years. Of the 517 patients, 188 (36%) received cisplatin-based regimens and 92 (18%) developed any stage AKI. Approximately 86% AKI were stage 1 AKI. In the univariable analyses, hypertension, impaired renal function, and cisplatin-based regimen were significantly associated with increased risk of AKI. In the multivariable analysis, hypertension, impaired renal function, and cisplatin-based regimen were independently and significantly associated with increased risk of AKI (Table). The optimal cutoff value of estimated glomerular filtration rate for AKI was 65.0 mL/min/1.73m^2. ROC analysis showed that the AUC of hypertension plus eGFR $<$65.0 mL/min/1.73m^2 plus cisplatin-based regimen was 0.748 (95% confidence interval [CI]: 0.697–0.799]. **Conclusions:** Hypertension, impaired renal function, and cisplatin-based regimens were risk factors for NAC-induced AKI in patients with MIBC. Research Sponsor: None.

Multivariable analysis.

	Factor	*P* value	Odds Ratio	95% CI
Age	Continuous	0.462	0.989	0.959–1.019
Hypertension	Presence	0.016	1.894	1.128–3.179
eGFR	Continuous	$<$0.001	0.955	0.939–0.971
Cisplatin	Positive	$<$0.001	6.530	3.725–11.45

Reasons for refusal of or ineligibility for radical cystectomy (RC) in patients (Pts) with bacillus Calmette-Guérin (BCG)–unresponsive high-risk non–muscle-invasive bladder cancer (HR NMIBC) from the SunRISe-1 study.

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Background: RC is the recommended treatment (tx) option for pts with BCG-unresponsive HR NMIBC. However, RC is associated with significant risk of morbidity, mortality, and impact on quality of life (QoL); some patients may refuse/be ineligible for RC. In a systemic review of 160 real-world studies, <20% of pts with HR NMIBC recurrent after BCG underwent RC (PMID 35046678). For RC-ineligible pts, bladder-sparing tx is recommended. TAR-200, a novel intravesical drug delivery system that provides sustained release of gemcitabine within the bladder, is under investigation in pts with BCG-unresponsive HR NMIBC who are ineligible for/refuse RC in the ongoing ph 2b SunRISe-1 (SR-1) study (NCT04640623). Preliminary results showed a promising complete response (CR) rate of 73% and durable responses in pts with BCG-unresponsive HR NMIBC treated with TAR-200 (Daneshmand et al. AUA 2023). We report reasons for refusal/ineligibility for RC in pts enrolled in the TAR-200 monotherapy cohort of SR-1. **Methods:** SR-1 is evaluating the efficacy and safety of TAR-200 + cetrelimab (CET; anti–PD-1) (Cohort 1 [C1]), TAR-200 alone (C2), or CET alone (C3). Pts ≥18 y with histologically confirmed carcinoma in situ (CIS) ± papillary disease (T1, high-grade Ta) who completed adequate BCG and recurred ≤12 mo since last BCG dose with ECOG performance status (PS) of 0-2 are randomized to C1, C2, or C3. As of Amendment 4, pts with papillary disease only will be enrolled in C4 with TAR-200 alone. The primary end point is overall CR rate at any time. Refusal/ineligibility for RC was documented in the electronic case report form. **Results:** As of Aug 24, 2023, 54 pts were treated in C2. Median age was 71 y (range 40-85). Pts had a median of 12 (range 7-42) prior BCG doses with a median of 3.0 mo (range 0.2-22.0) from last BCG dose to recurrence. Most pts (96%) had ECOG PS 0; 33% had CIS with papillary disease. 50%, 48%, and 19% of pts had a medical history of Gr ≥2 metabolic, vascular, and cardiac conditions, respectively, and 9% were current nicotine users. Overall, 51 (94%) pts refused RC; 3 (6%) were ineligible (Table). The most common reason for refusal was a preference for bladder preservation (52%), followed by concern about QoL (37%). Pts were ineligible for RC due to medical/surgical comorbidities (4%) and age (2%). **Conclusions:** Most pts enrolled in C2 of SR-1 refused RC, with preference for bladder preservation and QoL concerns being the most common reason for refusal. This highlights the need for bladder-sparing tx options for pts with HR NMIBC recurrent after BCG. Clinical trial information: NCT04640623. Research Sponsor: Janssen Research & Development.

Reasons for not receiving RC.

Pts with Reason, n (%)	Cohort 2 (N=54)
Ineligible	3 (6)
Medical/surgical comorbidities	2 (4)
Age	1 (2)
Refused RC	51 (94)
Preservation of bladder	28 (52)
QoL concerns post-RC	20 (37)
Mortality/morbidity concerns	2 (4)
Preservation of sexual function	1 (2)

Identification of patients with metastatic urothelial cancer not able to receive maintenance avelumab.

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Background: Maintenance avelumab following frontline platinum-based chemotherapy for metastatic urothelial cancer (mUC) is associated with survival benefit. Eligibility to receive avelumab maintenance requires receiving 4-6 cycles chemotherapy without disease progression. Not all patients complete 6 cycles of chemotherapy or meet eligibility to receive avelumab and these patients may need to have alternative therapies. Here we present real world data to assess whether baseline characteristics can be used to identify patients unable to complete 6 cycles of chemotherapy and whom may not be eligible for maintenance avelumab. **Methods:** This retrospective audit was performed at Barts Cancer Centre for consecutive patients from January 2010 until August 2023. Patients who received frontline gemcitabine and cisplatin/carboplatin chemotherapy for advanced mUC were included. Eligibility for avelumab is defined as completing 4-6 cycles of chemotherapy without disease progression (PD). Characteristics of patients completing 6 cycles of chemotherapy, versus those who do not were described. Chi-squared tests were conducted to compare characteristic between the two groups, using SPSS v28. **Results:** 265 patients receiving frontline systemic therapy were identified over a 13-year period. 242 (91%) received Gem/Cis or Gem/Carbo chemotherapy. 151 (63%) patients were eligible to receive maintenance avelumab. 91 (38%) patients were not eligible due to receiving less than 4 cycles chemotherapy (68%) or due to PD (75%), or both. 91 (38%) patients completed 6 cycles of chemotherapy. Having a low baseline Hb <100g/dl was the only baseline characteristic associated with receiving less than 6 cycles chemotherapy (p=0.002). 33% of patients who completed less than 6 cycles chemotherapy had a Hb <100g/dl, compared to 10% of the patients who completed chemotherapy (p=0.002). Any dose delays was associated with a lower likelihood of being eligible to receive avelumab (32% and 18% dose delays in avelumab eligible vs ineligible cohorts, respectively (p<0.001). Patients with any dose delays had more frequently received carboplatin (65% vs 39%, p=0.012) and had visceral metastases including liver metastases (63% vs 39%, p=0.014), compared to those without dose delays. **Conclusions:** Specific baseline factors predispose to an inability to deliver 6 cycles of chemotherapy without complications or progression. These patients are less likely to receive maintenance avelumab. These data help the optimise number of cycles offered to patients in mUC. Research Sponsor: None.

Factors predictive of primary resistance (PrimRes) to immune checkpoint inhibitors (ICIs) in patients (pts) with metastatic urothelial cancer (mUC).

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Background: Response rates to ICIs in pts with mUC remain modest at around 20% and there are no reliable biomarkers to select pts most likely to respond to ICI. It is an unmet need to define factors associated with PrimRes (progressive disease (PD) clinically and/or radiologically after at least 2 cycles of ICI) to spare pts from unnecessary treatment and the associated physical and financial toxicity. PrimRes to ICI has not been well defined in mUC pts and we sought to study predictive factors in our real-world cohort. **Methods:** We retrospectively reviewed 335 pts at the Cleveland Clinic who received ≥ 2 cycles or at least 6 weeks of ICI with pembrolizumab (P) or atezolizumab (A) between 2015 and 2023. Pt characteristics such as age, sex, race, BMI, primary site (bladder vs upper tract UC (UTUC)), and antibiotic (Abx) use before or after start of ICI and pre-treatment platelet to lymphocyte (PLR) ratios (divided into quartiles) were collected. PrimRes was defined as pts who had clinical and/or radiologic PD or death from disease within 14 weeks (time period of 1st assessment with imaging) of ICI initiation. Pts with PrimRes were compared to rest (responders, stable disease and subsequent PD). Multivariate cox regression models were used to identify factors associated with PrimRes. **Results:** Of the 335 pts, 129 (38.5%) pts had PrimRes based on our criteria. Median age was 73 yrs (35-95). PLR quartiles were clarified as (<149, 149-207, 207-308, ≥308). In our multivariate regression model, we found that pts with PLR ≥308 had a significantly higher chance of PrimRes compared to those with PLR <149 (Hazard Ratio (HR): 2.49; 95% CI: 1.22-5.15; p = 0.0133). Being underweight (BMI < 18.5) was associated with significantly higher rates of PrimRes than normal weight pts (HR: 6.91; 95% CI: 1.55-48.81; p = 0.0211). Abx use within 60 days post ICI start (HR: 2.29; 95% CI: 1.38-3.83; p = 0.0015) and UTUC (HR: 0.46; 95% CI: 0.25-0.83; p = 0.0099) were associated with PrimRes to ICI. **Conclusions:** In our large cohort of pts with mUC receiving ICI, we report that PLR ≥308, BMI < 18.5, use of Abx within 60 days post- ICI, and UTUC were associated with development of PrimRes to ICI. Ongoing genomic and immune correlates from tissues collected from our cohort will help us better understand the mechanisms of PrimRes to ICI. Validation and harmonization with more datasets and prospective studies can inform future steps towards patient-directed approaches. Research Sponsor: None.

Factor	Comparison	HR (95% CI)	P-value
PLR	≥308 vs. <149	2.48 (1.22, 5.15)	0.0133
Age≥	73 vs. <73 yrs	0.73 (0.44, 1.20)	0.217
BMI	Obese (≥ 30 kg/m^2) vs. Normal (18.5-24.9 kg/m^2)	0.99 (0.52, 1.88)	0.9815
	Overweight (25 -29.9 kg/m^2) vs. Normal	0.88 (0.49, 1.57)	0.6592
	Underweight (< 18.5 kg/m^2) vs. Normal	6.91 (1.55, 48.81)	0.0211
ABX within 60-day Post-IO	Yes vs. No	2.28 (1.38, 3.83)	0.0015
GU tract	Lower vs. Upper	0.46 (0.25, 0.83)	0.0099

Analysis of inactivating *TSC1* and *TSC2* alterations in advanced genitourinary (GU) cancers from a real-world patient population in the Foundation Medicine genomic database.

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Background: Identification of genetic alterations in cancer via genomic profiling may contribute to better outcomes for patients with advanced GU cancers. Patients with perivascular epithelioid cell tumors in AMPECT (NCT02494570), who had inactivating alterations in the tumor suppressor genes *TSC1* or *TSC2*, critical negative regulators of mTOR activity, had confirmed responses (8/9 patients with inactivating *TSC2* alterations and 1/5 patients with inactivating *TSC1* alterations) to the mTOR inhibitor *nab*-sirolimus. PRECISION 1 (NCT05103358), an enrolling tumor-agnostic study, is assessing *nab*-sirolimus in patients with advanced cancers bearing inactivating *TSC1* and/or *TSC2* alterations. We used data from a real-world genomic database to enumerate frequencies of *TSC1* and *TSC2* inactivating alterations in patients with GU cancers. **Methods:** Next-generation sequencing data from Foundation Medicine's database of 463,546 patients with advanced cancer (as of March 29, 2022) were analyzed using the FoundationInsights web-based platform to identify inactivating *TSC1* or *TSC2* alterations in patients with GU cancers. *TSC1* or *TSC2* alterations were categorized as short variants [base substitutions, insertions and deletions], rearrangements, and copy number deletions. Tumors with these alterations were also evaluated for mutations in other genes, tumor mutational burden (TMB), and microsatellite instability status. **Results:** Of patients in the database, 9.6% of those with bladder cancer, 5.2% of those with kidney cancer, and 0.7% of those with prostate cancer had inactivating *TSC1* or *TSC2* alterations. Overall, inactivating *TSC1* or *TSC2* alterations were present in 1518 of the 36,920 patients with GU cancers. A majority of these 1518 patients (74%) were male and most (78%) were 51–80 years of age at the time the sample was obtained. Of samples with inactivating *TSC1* and *TSC2* alterations (n=1518), 84.9% were in *TSC1* and 15.7% were in *TSC2*; alterations included short variants (76.7% and 12.2 %), rearrangements (2.4% and 2%), and copy number deletions (5.6% and 1.3%), respectively. TMB was low (<6 mutations/megabase) in 52% of tumors and most (89%) were microsatellite stable. Other commonly mutated genes in this cohort with *TSC1* or *TSC2* inactivating alterations were *TERT* (64.4%), *TP53* (44.1%), and *CDKN2A* (40%). **Conclusions:** Inactivating *TSC1* and/or *TSC2* alterations commonly occurred in GU cancers. A proportion of GU tumors have a low TMB and/or are microsatellite stable, suggesting that *TSC1* and *TSC2* inactivating alterations may be driver mutations rather than passenger mutations in those tumors. Therefore, patients with inactivating alterations in *TSC1* or *TSC2* may benefit from mTOR inhibition via *nab*-sirolimus. This hypothesis is being tested in the PRECISION 1 study which is open for enrollment of patients with *TSC1* or *TSC2* alterations. Research Sponsor: Aadi Bioscience.

ABLE-41: Nadofaragene firadenovec-vncg early use and outcomes in a real-world setting in the United States.

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Background: Approximately one-third of patients with non–muscle-invasive bladder cancer (NMIBC) initially responding to Bacillus Calmette-Guérin (BCG) experience recurrence and/or progression in the first year after treatment.[1] Local, effective, bladder-preserving options are needed for patients with BCG-unresponsive NMIBC. Nadofaragene firadenovec-vncg is the first FDA-approved intravesical gene therapy for treatment of high-risk BCG-unresponsive NMIBC with carcinoma in situ (CIS) ± papillary tumors. In a single-arm, multicenter, open-label, repeat-dose, phase 3 study, 53.4% of patients (55/103) with CIS ± high-grade Ta/T1 BCG-unresponsive NMIBC achieved complete response (CR) 3 months after the first instillation of nadofaragene firadenovec.[2] The safety profile of nadofaragene firadenovec was manageable, with 103 (66%) patients reporting mild (grade 1/2) study drug-related adverse events (AEs). Six (3.8%) patients had grade 3/4/5 study drug-related AEs. ABLE-41 (NCT06026332) is an observational study evaluating the effectiveness, overall experiences, patterns of use, and safety in patients treated with nadofaragene firadenovec in a US real-world setting. **Methods:** This noninterventional study includes approximately 50 urology sites in the U.S. with anticipated enrollment of 800 patients. Adults ≥18 years with prescribed and scheduled treatment with nadofaragene firadenovec per physician discretion or those who received their first instillation of nadofaragene firadenovec per physician discretion after September 5, 2023, but before site activation are eligible to enroll. The primary objective is to assess the effectiveness of nadofaragene firadenovec measured as the CR rate as determined by investigator. Secondary outcomes include: nadofaragene firadenovec patterns of use; duration of CR, recurrence-free survival, cystectomy-free survival, progression-free survival, overall survival, and bladder cancer–specific mortality; patient, caregiver and physician experiences; adjunctive use of molecular markers; and safety. Patient and caregiver experiences will be assessed using the respective EuroQol 5 Dimension 5 Level questionnaire and Work Productivity and Activity Impairment questionnaire, adapted for caregiving. Patients and caregivers will be surveyed before all nadofaragene firadenovec administrations. Physicians will be surveyed 1, 12, and 24 months after first patient first instillation. All AE data will be collected starting from index date. The estimated follow-up period is 24 months, until study discontinuation, or withdrawal. Final results from this large, prospective, multi-institutional, real-world registry providing early use and outcomes of nadofaragene firadenovec are expected December 2026. References: 1. Sylvester RJ et al. *Eur Urol.* 2010;57:766-73; 2. Boorjian SA et al. *Lancet Oncol.* 2021;22:107-17. Clinical trial information: NCT06026332. Research Sponsor: Ferring Pharmaceuticals, Inc.

The "Get Moving Trial": A phase I/II RCT of home-based (P)rehabilitation ((P)REHAB) with ExerciseRx in muscle-invasive bladder cancer (MIBC)—Study protocol for a randomized controlled trial.

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Background: Patients with MIBC often have a high burden of frailty, sarcopenia, mobility impairment, and multimorbidity, each of which is associated with reduced treatment tolerability. Prehabilitation programs are designed to improve functional capability prior to treatment to mitigate functional decline and optimize outcomes. Barriers to widespread adoption include cost, time, intensity of in-person interventions, and overly restrictive inclusion criteria which would exclude most patients with MIBC. Here, we describe a randomized controlled trial to evaluate the feasibility, usability, and impact of a pragmatic (P)REHAB exercise intervention delivered via the ExerciseRx app in participants with MIBC undergoing neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC). The primary objectives are to evaluate the (P)REHAB intervention vs. standard care (SC) to quantify the efficacy of the intervention to 1) improve or maintain physical function in patients with MIBC undergoing NAC followed by RC, and 2) globally characterize the impact of the (P)REHAB intervention with respect to patient-reported feasibility and acceptability, health-related quality of life, body-composition, frailty, treatment-associated and clinical outcomes. **Methods:** We will recruit and randomize 102 patients in a 1:1 ratio to the (P)REHAB or SC arms. The (P)REHAB arm will be prescribed a personalized, home exercise program (~20-minutes, 4x weekly) via the ExerciseRx app, during NAC, prior to RC and for 90-days post-RC as well as graded progression in step count. SC participants will receive printed guideline-based recommendations for physical activity during standard perioperative care. ExerciseRx comprises of 1) a provider dashboard integrated into the electronic health record for prescribing exercises and monitoring patient progress, and 2) a patient app, that administers exercise plans and tracks exercise repetitions using sensors in commodity smart devices. Step count in the (P)REHAB and SC arm will be tracked with Fitbit trackers. In the (P)REHAB arm, step count data from the Fitbit will be reviewable in the ExerciseRx provider dashboard and patient app. Eligibility criteria: English-speaking adults (>18 years) with AJCC pT2-4 N0-1 M0 MIBC planning to undergo NAC followed by RC who are willing and able to participate in the trial. Primary outcome: Change in the Short Physical Performance Battery. Secondary outcomes: FitBit-assessed step count and sedentary time, ExerciseRx adherence and usability, patient-reported quality of life (EORTC-QLQ-C30, -BLM30), change in body composition (fat-mass, fat-free mass), frailty (Cancer and Aging Resilience Evaluation), treatment-associated adverse events between baseline and following NAC, and 3 months following RC. Trial enrollment will commence 10/2023. Clinical trial information: NCT06040762. Research Sponsor: Bladder Cancer Advocacy Network.

TPS707 Trials in Progress Poster Session

Intravesical recombinant BCG followed by perioperative chemo-immunotherapy for patients with muscle-invasive bladder cancer (MIBC): A multicenter, single arm phase 2 trial (SAKK 06/19).

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Background: The integration of immune checkpoint inhibitors (ICI) in the perioperative setting of localized muscle-invasive bladder cancer (MIBC) is extensively investigated and several results from phase 2 trials have been published. While promising, the pathological complete remission rate (pCR, ypT0 ypN0) achieved with ICI-containing regimens appears similar to cisplatin-based chemotherapy alone. Further improvement is needed. Intravesical BCG has successfully been used for decades for non-muscle invasive bladder cancer (NMIBC) in patients (pts) with carcinoma in situ (CIS) and as adjuvant treatment for high-risk papillary tumors. Intravesical BCG induces a local inflammation leading to induction of the innate immune system, probably followed by a tumor-specific adaptive immune response. Recently, a novel recombinant BCG vaccine (VPM1002BC) has been developed and a clinical study in BCG-refractory NMIBC (SAKK 06/14, Eur Urol Oncol. 2022 Apr;5(2):195-202.) has demonstrated good safety with low local toxicity and promising efficacy. We hypothesize that induction therapy with intravesical VPM1002BC improves the efficacy of systemic perioperative chemo-immunotherapy in pts with operable MIBC. **Methods:** SAKK 06/19 is an open-label single arm phase II trial for pts with operable pT2 or cT2-T4a cN0-1 MIBC without contraindication for cisplatin. Prior intravesical BCG is excluded as are pts unable to keep BCG instillation for less than 1 hour. Intravesical VPM1002BC is administered weekly for 3 instillations. Atezolizumab (atezo) 1200mg is given on day 1 and then every 3 weeks (q3w) for four times. Chemotherapy with cisplatin (70mg/m2 day 1) and gemcitabine (1000mg/m2 day 1 & 8) q3w is started on day 22 and given for four cycles followed by radical cystectomy and lymphadenctomy. Atezo is continued after surgery for 13 cycles in case of residual muscle invasive disease (≥ypT2) or positive lymph nodes (ypN+) only. pCR at cystectomy is the primary endpoint. A total of 46 pts is needed (including 15% dropout rate) using Simon's minimax two-stage design with type I error 5%, power 80%, a null hypothesis of ≤35% pCR and an alternative hypothesis of ≥55% pCR. Secondary endpoints include pathological response rate (<ypT2N0), event-free survival, recurrence-free survival, overall survival, feasibility and toxicity. An interim safety analysis will be performed after the first 12 pts have completed neoadjuvant treatment specifically assessing toxicity possibly associated with intravesical BCG application. An interim efficacy analysis will be performed after the first 21 pts have undergone surgery. Accrual to the study is currently ongoing (NCT04630730). Clinical trial information: NCT04630730. Research Sponsor: Roche.

New phase 1 SURPASS trial cohort: Early-line ADP-A2M4CD8 T-cell receptor T-cell therapy plus pembrolizumab in urothelial carcinoma.

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Background: ADP-A2M4CD8 T-cell receptor (TCR) T-cell therapy consists of autologous CD4+ and CD8+ T-cells genetically modified to target melanoma-associated antigen A4 (MAGE-A4) in patients (pts) with advanced cancers who are human leukocyte antigen A*02 eligible. In the late-line setting, ADP-A2M4CD8 monotherapy has demonstrated an acceptable benefit-to-risk profile and clinical responses across multiple tumor types in the ongoing Phase 1 SURPASS trial (NCT04044859). As of November 23, 2022, there were encouraging signs of antitumor activity in the 7 pts with advanced urothelial carcinoma (UC) treated in SURPASS, with best overall responses of 1 complete response, 3 partial responses, and 3 stable disease, giving an overall response rate of 57.1% and a disease control rate of 100% (Aggen DH. et al., Poster 517, ASCO-GU 2023; San Francisco, CA, USA). Furthermore, inhibiting immunosuppressive pathways may enhance antitumor activity. Thus, a new SURPASS cohort consisting of early-line ADP-A2M4CD8 TCR T-cell therapy combined with pembrolizumab in participants with UC has been opened. **Methods:** A dedicated UC cohort will enroll ≤15 pts with unresectable locally advanced or metastatic UC who have received first-line cisplatin-based standard-of-care (SOC) chemotherapy and are either currently receiving second-line SOC pembrolizumab or have received avelumab maintenance therapy and no second-line therapy. Key eligibility criteria include >30% of tumor cells expressing MAGE-A4 (≥2+ by immunohistochemistry); positivity for HLA-A*02:01, 02:02, 02:03, or 02:06 alleles; measurable disease per RECIST v1.1 prior to lymphodepletion; and ECOG performance status of 0 or 1. T-cells are collected by leukapheresis, transduced with a lentiviral vector expressing the MAGE-A4-specific TCR and an additional CD8α co-receptor designed to increase functionality of CD4+ T-cells, and expanded ex vivo. Pts receive lymphodepletion chemotherapy consisting of cyclophosphamide 600 mg/m^2/day for 3 days and fludarabine 30 mg/m^2/day for 4 days followed by ADP-A2M4CD8 infusion (1x10^9 to 10x10^9 transduced T-cells) and subsequent pembrolizumab 400 mg (administered every six weeks for ≤2 years, until unacceptable toxicity or disease progression). Primary and secondary endpoints include evaluation of adverse events (AEs), serious AEs, AEs of special interest, and overall response rate per RECIST v1.1 by investigator review, respectively. Trial registration number: NCT04044859. Editorial acknowledgement:This study is sponsored by Adaptimmune (Philadelphia, PA, USA). Writing and editorial support was from Excel Scientific Solutions (Fairfield, CT, USA); funding was provided by Adaptimmune. Clinical trial information: NCT04044859. Research Sponsor: Adaptimmune (Philadelphia, PA, USA).

TPS709 Trials in Progress Poster Session

A phase 1, first-in-human, dose-escalation and expansion study of FX-909 in patients with advanced solid malignancies, including advanced urothelial carcinoma.

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Background: High Expression of Peroxisome proliferator-activated receptor gamma (PPARG), a nuclear receptor-family transcription factor, drives the initiation and development of UC in luminal molecular subtype tumors. Genetic profiling of UC has identified recurrent oncogenic alterations in the PPARG transcriptional complex, including focal amplification, missense mutations, and fusions in the heterodimeric partner of PPARG, the retinoid X receptor alpha (RXRA). High levels of PPARG expression and recurrent oncogenic alterations are observed in other solid malignancies including colorectal, gastroesophageal, pancreatic and lung cancers. FX-909 is an oral, first-in-class, new molecular agent that specifically, potently, and covalently modifies PPARG to mediate basal and ligand-activated transcription. Treatment of genetically defined UC xenografts with FX-909 has shown an 84% tumor growth inhibition (TGI) at a dose expected to be equivalent to 50 mg dose in humans, which is the starting dose in this clinical study. **Methods:** FX-909-CLINPRO-1 (NCT05929235) is a first-in-human, multicenter, open-label Phase 1 study to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary clinical activity of FX-909 given orally in patients with advanced solid malignancies. Patients enrolled in the trial must have ECOG performance status $\leq$2 and must be $\geq$ 18 years of age. Initially, FX-909 will be given once daily to patients with any advanced solid malignancy in a dose-escalation phase (Part A) utilizing a 3+3 design. Five dose cohorts of 3 to 6 patients are planned. At the time of submission, three patients are enrolled in Part A- cohort one, 50mg. Additional patients will be allowed to backfill to previously cleared dose levels that demonstrate therapeutically relevant exposures or evidence of clinical activity. Once a RP2D has been determined, a monotherapy expansion phase (Part B) will proceed in a Simon 2-stage design in patients with locally advanced (unresectable) or metastatic UC with measurable disease and tumors harboring defined genetic alterations in PPARG, RXRA and FGFR3 (Motley et al, 2022). In stage 1, up to 19 evaluable patients will be enrolled. If $\geq$4 objective responses are observed, enrollment will continue into Stage 2 with an additional 14 evaluable patients. One treatment cycle is 28 days. Dose expansion will evaluate the safety, PK/PD profile, and antitumor activity of FX-909 at the RP2D. Exploratory objectives include the evaluation patient selection biomarkers from tissue and blood samples. FX-909 clinical activity will be assessed using RECIST v1.1 criteria. The study is currently enrolling patients in the US. Clinical trial information: NCT05929235. Research Sponsor: None.

TPS710 Trials in Progress Poster Session

INVEST: A phase Ib window of opportunity study of atezolizumab administered either intravesically or direct tumour injection in patients with bladder cancer prior to radical cystectomy.

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Background: High-risk non-muscle invasive bladder cancer is a common and difficult to manage disease. The treatment of choice is radical cystectomy (RC), as BCG-unresponsive tumours have a poor prognosis. RC negatively impacts health related quality of life and therefore clinicians have explored alternative treatments. The FDA approved systemic pembrolizumab for BCG-refractory carcinoma in situ, but uptake is low, reflecting concerns around efficacy and safety for a non-invasive cancer. We hypothesize that intravesical administration of a PDL1 inhibitor could be effective with less systemic toxicity. However, it is unknown whether antibodies delivered via this route can reach the tumour vasculature. INVEST is a phase Ib window of opportunity study aiming to investigate the safety and preliminary activity of both passive instillation and direct injection into the tumour/bladder wall of intravesical atezolizumab prior to RC. **Methods:** Eligible participants (ECOG performance status 0-2) are awaiting RC for urothelial cell carcinoma of the bladder (any stage). Those with muscle invasive cancer must be ineligible for or refuse cisplatin based neo-adjuvant chemotherapy. RC will not be delayed by study treatment. Each dose confirmation stage uses a conventional 3+3 design to establish safety based upon dose limiting toxicities. The recommended single dose will be determined first of either 600mg or 1200mg (n=3-12). This dose will then be evaluated further to determine the recommended multiple dose of either 600mg or 1200mg administered weekly for 3-6 weeks (n=3-12). A dose expansion stage will then treat 10 patients at the recommended multiple dose to further evaluate safety and toxicity. This schema will be followed independently for both the passive instillation and direct injection routes of intravesical atezolizumab administration. Efficacy signals will be explored via progression-free survival at two years and pathological complete response rate. INVEST will assess the pharmacokinetic profile of intravesical atezolizumab, anti-drug antibodies to atezolizumab. Samples are being prospectively collected for future translational research. Sampling (fresh, frozen, and FFPE blocks) of scar, tumour and background urothelium is being performed on cystectomy specimens. Tissue microarrays will be created from TURBT and cystectomy tissue. Translational samples include pre- and post-treatment blood cfDNA, PBMCs and serum and urine cfDNA. We will assess drug penetration into the bladder wall and the effects of treatment on circulating tumour cells, and local and systemic immune cell composition. Enrolment began in May 2023. This is a single-site UK-based study and we are not currently seeking additional recruiting centres. Clinical trial information: ISRCTN15842444. Research Sponsor: Roche.

Guiding adjuvant instillation in intermediate-risk non-muscle invasive bladder cancer by drug screens in patient-derived organoids.

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Background: Recurrence rates in intermediate risk non-muscle invasive bladder cancer (NMIBC) are high and therefore, clinical guidelines recommend adjuvant instillations. However, the exact regimen with an exact number of instillations and the chemotherapeutic agent to be used are not clearly defined. During the last years we have established a standardized pipeline to generate patient-derived organoids (PDO) from cold cup biopsies of NMIBC. We showed that the subsequent organoids maintain key features of the parental tumor and share the molecular landscape. Moreover, our pipeline allows to investigate drug response to different agents in a standardized manner. **Methods:** In this ongoing, open-label, single center phase II trial, we aim to use drug screens in PDO of patients with intermediate risk NMIBC to guide drug selection for intravesical instillation. Patients with diagnosis of intermediate-risk NMIBC are enrolled. PDO are generated from biopsies prior transurethral resection of the bladder tumor. On the generated PDO drug response is determined to four chemotherapeutic agents that have already been used for bladder instillations in the literature (Epirubicin, Mitomycin C, Gemcitabine and Docetaxel). The most effective drug is selected for adjuvant instillation into the bladder once weekly for 6 instillations. The follow-up thereafter is performed according to European guidelines. The primary endpoint of the study is to determine the proportion of patients for which a specific selection of chemotherapeutic agent for intravesical instillation can be determined by using drug screens in PDOs. Secondary endpoints are recurrence- and, progression free survival, quality of life and translational studies. The null hypothesis, that a drug prediction will only be possible in 65% of patients, will be tested against a one-sided alternative. Assuming that the real proportion is 85%, 31 participants should show a statistically significant result at 5% significance and 80% power (exact binomial test). Due to early termination of 10%, a total number of 34 patients will be included. We are successfully conducting a trial to implement drug screens in PDO into daily routine and to guide patient treatment. This is a novel concept to precise treatment selection in patients with intermediate-risk NMIBC. When the primary endpoint is met, a modification of the trial with larger sample size, novel compounds and a focus oncological outcomes is foreseen. Clinical trial information: NCT05024734. Research Sponsor: None.

TPS712 Trials in Progress Poster Session

Neutralizing GDF-15 in muscle-invasive bladder cancer (MIBC): A neoadjuvant immunotherapy trial of visugromab (CTL-002) in combination with the anti-PD1 antibody nivolumab (GDFather-Neo).

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Background: Neoadjuvant chemotherapy (NACT) is a well-established treatment modality in MIBC but suffers from limited activity and significant toxicity. Neoadjuvant immunotherapy (I/O) demonstrated clinical safety and efficacy in various solid tumors including MIBC, with potentially less toxicity. Results from previous studies of single-agent I/O indicated a proportion of pathologic complete responses (ypT0N0) similar to that reported with NACT. Therefore, improving ypT0N0 responses remains a major task for treatment of MIBC. Increasing evidence emerged that Growth and Differentiation Factor 15 (GDF-15) plays a critical local immunosuppressive role. Apart from blocking immune-cell entry into tissues GDF-15 also has major impact on the formation of the immune synapse. Many tumors overexpress GDF-15 and have hijacked this mechanism to block I/O therapy success. Various translational research efforts indicated that GDF-15 may play a significant role for immunosuppression and T-cell exclusion in urothelial carcinoma (UC). Visugromab (CTL-002) is a GDF-15 neutralizing IgG4 monoclonal antibody that demonstrated in Phase 1 a favorable safety profile and promising clinical activity with durable and deep responses in PD-1/PD-L1 relapsed/refractory metastatic solid tumors in combination with the anti-PD1 antibody Nivolumab (Nivo)*. The Neo-GDFather trial is intended to investigate the combination of Visugromab with Nivo vs. Nivo monotherapy as neoadjuvant therapy for MIBC in patients (pts) who are ineligible for or elect not to undergo NACT. Primary endpoints are the complete pathologic response rate and radiologic response. **Methods:** Multi-center, parallel-cohorts and single-blinded Phase 2 study of neoadjuvant therapy in pts planned for radical cystectomy (RC). A total number of 30 subjects with stage T2-T4N0M0 MIBC will be enrolled and assigned 1:1 to receive either Nivo + Visugromab or Nivo + Placebo after stratification for CPS PD-L1 expression and cT-stage. Other inclusion criteria comprise an ECOG performance status 0-1 and a pure/predominant UC histology. No statistical assumptions were undertaken at this stage.Treatment consists of three 4-week cycles [i.v., Q4Wk], and RC is planned 4-8 weeks after last dose of study drug. After RC, pts will follow standard recommendations of EAU guidelines. Primary endpoints are the proportion of ypT0N0 response and radiologic response rate. Secondary endpoints comprise additional efficacy parameter, surgical and medical safety, PK and PD assessments. Translational research includes evaluation of immunologic parameters in the tumor, other immune-correlates and molecular profiles, as well as evaluation of treatment-emergent cytokine and chemokine profiles in peripheral blood. * Melero *et al.*, #2501 ASCO Annual Meeting 2023 Oral Abstract Session. Clinical trial information: Not yet available. Research Sponsor: CatalYm GmbH.

TPS713 Trials in Progress Poster Session

Phase I/II study of ipilimumab plus nivolumab (IPI-NIVO) combined with sacituzumab govitecan in patients with metastatic cisplatin-ineligible urothelial carcinoma.

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Background: Treatment options are suboptimal and limited for cisplatin-ineligible metastatic urothelial carcinoma (mUC) patients. Sacituzumab govitecan (SG) is a Trop-2 directed antibody-drug conjugate (ADC) coupled with SN-38 through a hydrolysable linker. In the phase II TROPHY-U-01 study, SG demonstrated an objective response rate (ORR) of 27% and median overall survival (OS) of 10.5 months in mUC patients who progressed after platinum-based chemotherapy and immune checkpoint inhibitors (ICI), receiving accelerated approval by the US FDA. In CheckMate 032 study, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (N1+I3) every 3 weeks (Q3W) x 4 cycles followed by nivolumab monotherapy 3mg/kg Q2W showed promising activity post-platinum that led to the ongoing phase III trial in the first-line setting (NCT03036098). Given potential synergism between immunogenic cell death induced by ADC and ICI, we hypothesized that the combination of SG and IPI-NIVO would benefit patients with manageable toxicities. We designed this study to assess the safety and clinical activity of IPI-NIVO with SG as first-line therapy for cisplatin-ineligible mUC patients. **Methods:** This is an ongoing phase I/II, single arm, multicenter study for cisplatin-ineligible mUC. The Phase I portion enrolled 9 patients using a 3+3 design with safety and RP2D as primary endpoints. In this part, patients received fixed doses of IPI-NIVO (N1+I3) IV Q3Wx 4 cycles combined with SG (DL1 8 mg/kg or DL2 10mg/kg) IV on days 1, 8 Q3W x 4 cycles. This was followed by maintenance nivolumab 360 mg IV Q3W with SG on days 1, 8 Q3W. The RP2D of SG was determined as 8 mg/kg and combination was deemed safe and tolerable. ORR is the primary endpoint in the ongoing phase II portion of the study using Simon 2 stage design (n=34) with a futility interim analysis after 13 patients. The null hypothesis of ORR $\leq$ 38% will be tested with a desirable ORR of $>$60% under a statistical power of 80% and a one-sided type I error rate of 5%. Thirteen of the 34 patients have been enrolled and the study has passed the predefined interim analysis for futility. We aim to continue accrual. Exploratory biomarker analyses will be conducted using tumor and blood samples collected during screening and at progression. Clinical trial (NCT04863885). Clinical trial information: NCT04863885. Research Sponsor: BMS, Gilead.

MAIN-CAV: Phase III randomized trial of maintenance cabozantinib (CABO) and avelumab (Av) vs Av after first-line platinum-based chemotherapy in patients (pts) with metastatic urothelial cancer (mUC; Alliance A032001).

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Background: 1st-line induction platinum-based chemotherapy followed by switch maintenance Av is the current preferred standard of care in patients (pts) with aUC who do not progress after platinum-based chemotherapy. There is an significant need to further improve outcomes by combining Av with an effective, non-cross resistant therapy with non-overlapping toxicity. CABO is an oral inhibitor of MET, VEGFR and TAM family receptors involved in tumor growth, angiogenesis and immune cell regulation and has shown efficacy in UC in combination with PD-1/PD-1L1 inhibitor. We hypothesized that CABO-Av combination would improve survival vs Av alone and have an acceptable safety profile as switch maintenance therapy in mUC. **Methods:** MAIN-CAV is a phase III randomized, multicenter, international trial for pts with locally advanced/metastatic UC (including cN3M0 only)) who do not progress after 4-6 cycles of any platinum-based chemotherapy (gem-cis, gem-carbo, MVAC or ddMVAC). 654 adults are randomized 1:1 within 3-10 weeks (wk) after last dose of chemotherapy to receive Av 800 mg IV every 2 wk or Av and CABO 40 mg daily for up to 2 yrs. Key eligibility criteria include ECOG PS 0-1, no prior use of anti-PD(L)1, no CNS metastases, no major surgery within 4 wks, no uncontrolled hypertension or cardiovascular disorders. Pts are stratified based on 1) best response to 1L chemotherapy: complete vs partial response vs stable disease and 2) presence vs absence of visceral metastases. The primary endpoint is overall survival (OS) with assumptions of 1-sided alpha 0.025, power 80%, median OS 21 months (mo) with Av and hazard ratio 0.75, thus hypothesizing median OS 28 mo on CABO-Av. Key secondary endpoints include progression-free survival, safety, tolerability, and efficacy of CABO-Av vs Av alone based on RECIST 1.1 and iRECIST criteria (and PD-L1 status).Quality of life (QOL) are assessed using EQ-5D-5L, PROMIS-Fatigue 4a, EORTC QLQ-C30, EORTC QLQ-BLM30 between pts on CABO-Av vs Av alone. Biomarkers of response and resistance to Av will be assessed using baseline archival tissues, baseline and serial blood, ctDNA, stool and urine. Imaging studies will test the correlation of established and new radiomic signatures with survival, adverse events and QOL and incorporate both radiologic and biologic features to assess their potential association with outcomes. This trial would be the first to systematically address whether adding the multitargeted TKI, CABO, to Av improves survival vs Av alone as 1L maintenance therapy. https://acknowledgments.alliancefound.org. Support: U10CA180821, U10CA180882; U24CA196171, U10CA180863 (CCTG); Clinical trial information: NCT05092958. Research Sponsor: None.

TPS715 Trials in Progress Poster Session

PIVOT-006: A phase 3, randomized study of cretostimogene grenadenorepvec versus observation for the treatment of intermediate risk non-muscle invasive bladder cancer (IR-NMIBC) following transurethral resection of bladder tumor (TURBT).

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Background: Guidelines for Intermediate Risk Non-Muscle Invasive Bladder Cancer (IR-NMIBC) recommend adjuvant intravesical (IVE) therapy or surveillance. Despite this, 30–60% of patients still recur, and these Guideline recommendations are lacking level-1 evidence. Thus, there is a considerable gap in knowledge and an unmet medical need for improved therapies in the adjuvant setting. Cretostimogene Grenadenorepvec is an oncolytic adenovirus designed to preferentially replicate in and kill cancer cells. The vector is transcriptionally regulated by the E2F promoter that is up-regulated in retinoblastoma (Rb) pathway-defective tumor cells, common in most IR-NMIBC bladder tumors. Additionally, the virus is engineered to selectively express GM-CSF, in order to induce a robust systemic anti-tumor immune response. PIVOT-006 is an open-label, multi-center, randomized Phase 3 study designed to assess the efficacy and safety of intravesical Cretostimogene after TURBT versus TURBT alone. **Methods:** Eligibility criteria: age ≥18 years, Eastern Cooperative Oncology Group performance status of 0-2, histologically confirmed IR-NMIBC with absence of nodal or metastatic disease at screening. IR-NMIBC, as defined by American Urologic Association-Society of Urologic Oncology Guidelines on NMIBC, is either a Low Grade (LG) stage Ta tumor that recurs within 12 months of prior LG or High Grade (HG) bladder cancer, a solitary LGTa tumor >3cm in size, multifocal LGTa tumors, primary HGTa lesion < 3cm in size, or a LGT1 tumor. Participants will be stratified by receipt of perioperative chemotherapy and tumor grade. Pts (N~450) will be randomized 1:1 to receive intravesical Cretostimogene (Cohort 1) adjuvant to TURBT or TURBT alone (Cohort 2). Single dose perioperative intravesical chemotherapy at the time of TURBT is permitted. If intravesical NMIBC recurrence is noted in Cohort 2, participants will be eligible to receive intravesical Cretostimogene. In Cohort 1, intravesical Cretostimogene will be instilled in combination with n-dodecyl-B-D-maltoside (DDM, an inactive detergent) for 6 weekly doses during the induction phase, followed by 3 weekly maintenance cycles at months 3 and 6, and culminating in single intravesical doses at months 9 and 12. Primary disease assessments include serial cystoscopy, urine cytology, axial imaging, and centralized review of pathologic samples. The primary outcome measure is recurrence free survival. Secondary outcome measures include safety, tolerability, progression free survival, and time to next intervention. Exploratory outcome measures include patient-reported quality of life, biomarker analyses, coxsackie adenovirus receptor and E2F promoter expression, neutralizing antibodies, and markers of immunogenicity. Clinical trial information: Pending. Research Sponsor: CG Oncology.

A phase 1 study of IO102-IO103 vaccine plus pembrolizumab in patients with BCG-intolerant or unresponsive non-muscle invasive bladder cancer (NMIBC).

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Background: Pembrolizumab, an anti-PD1 antibody, is a treatment option for high-risk BCG-unresponsive NMIBC, but has a modest complete response (CR) rate of 41% at 3 months, and a median duration of CR of 16.2 months. IO102-IO103 is a novel immune-modulating cancer vaccine that stimulates activation of T cells targeting indoleamine-2,3-dioxygenase 1 (IDO1) and PDL1-positive cells, resulting in potentially increased susceptibility to anti-PD-1 blockade. Combination IO102-IO103 with nivolumab showed encouraging clinical activity and tolerability in previously anti-PD-1 naïve metastatic melanoma patients (NCT03047928). The existing data for synergistic effects of IO102-IO103 in combination with anti-PD1 therapy and the known expression of IDO in urothelial carcinoma lend rationale to this phase I trial designed to assess the feasibility, safety, and toxicity of IO102-IO103 plus pembrolizumab in patients with BCG-intolerant or unresponsive NMIBC. **Methods:** This open-label, single arm, phase 1 study enrolls patients with BCG-unresponsive or intolerant high-risk NMIBC who are ineligible for or have declined cystectomy and have adequate ECOG performance status (0-2), hematologic function, and end organ function. High-risk NMIBC is defined as T1, high-grade Ta, or CIS/Tis, with predominantly urothelial cell histology. Exclusion criteria include known active autoimmune disorders requiring immunosuppressive therapy or prior checkpoint inhibitor therapy. Eligible patients will be treated with pembrolizumab 200 mg IV on Day (D) 1, and IO102-IO103 85 mcg SQ on D1 and 8 of a 21-day cycle for the first two cycles, after which IO102-IO103 dosing will be D1 only, with treatment for up to 2 years. The primary endpoints of feasibility, safety, and toxicity will be evaluated by CTCAE v5.0 criteria and will be met if $\geq$10 patients out of 12 are able to complete the first cycle without experiencing pre-specified treatment-limiting toxicities. Key secondary endpoints include CR rate at 3 months, median duration of response, and cystectomy-free survival at 18 months. Biopsy specimens and serial urine and blood samples will be collected to evaluate potential biomarkers of response. Clinical trial information: NCT05843448. Research Sponsor: UC Davis Comprehensive Cancer Center; Christine & Helen Landgraf Memorial Research Award; IO Biotech.

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

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Background: Locally advanced or metastatic urothelial carcinoma (la/mUC) is an aggressive disease. Platinum-based chemotherapy has been the standard first-line (1L) therapy, but novel biomarker-informed strategies are attractive to improve outcomes. Human epidermal growth factor receptor 2 (HER2) expression (immunohistochemistry [IHC] 1-3+) has been reported in approximately half of all patients in multiple tumor types, including UC, and may be associated with poor outcomes. Disitamab vedotin (DV; RC48-ADC) is an investigational antibody-drug conjugate comprising a fully humanized HER2-directed monoclonal antibody, disitamab, conjugated to monomethyl auristatin E (MMAE) via a protease-cleavable mc-vc linker. DV elicits antitumor activity through multimodal mechanisms of action, including MMAE-mediated direct cytotoxicity, bystander effect, and immunogenic cell death. DV has shown encouraging activity with a consistent safety profile in a Chinese population of patients with la/mUC, both as a single agent in a post-platinum setting and in combination with a programmed cell death protein 1 (PD-1) inhibitor in the 1L setting. In the ongoing RC48-C014 phase 1b/2 study, DV + toripalimab demonstrated an objective response rate (ORR) of 83.3% in patients with HER2 IHC 2/3+ la/mUC and an ORR of 64.3% in those with IHC 1+ tumors. These data provide a robust rationale for this phase 3 trial of DV plus pembrolizumab in the 1L setting for HER2-expressing la/mUC. **Methods:** DV-001 (NCT05911295) is an open-label, randomized, multicenter, controlled phase 3 trial evaluating DV with pembrolizumab vs chemotherapy in patients with previously untreated HER2-expressing la/mUC. Patients will be randomized 1:1 to Arm A or B. Those in Arm A will receive DV intravenously (IV) every 2 weeks and pembrolizumab IV every 6 weeks. Patients in Arm B will receive platinum-containing chemotherapy with gemcitabine IV on Days 1 and 8 of every 3-week cycle, and either cisplatin or carboplatin on Day 1 of every 3-week cycle. Maintenance therapy with avelumab may be used where approved and available after completion of 4-6 cycles of 1L platinum-based chemotherapy, if clinically appropriate. Patients must have previously untreated la/mUC, measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1, Eastern Cooperative Oncology Group performance status score of 0-2 and be eligible for platinum-containing chemotherapy. HER2 expression must be determined using the VENTANA 4B5 HER2 IHC Assay at a central laboratory and using the most recent archival or fresh tumor sample. Primary endpoints include progression-free survival per blinded independent central review and overall survival. Enrollment is currently ongoing in the United States and planned globally. Clinical trial information: NCT05911295. Research Sponsor: None.

WUTSUP-02-II-Neo-Dis-Tis: Investigating the efficacy and safety of neoadjuvant tislelizumab plus disitamab vedotin with adjuvant tislelizumab in upper urinary tract carcinoma—A phase II multi-center study.

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Background: Upper tract urothelial carcinoma (UTUC) and urothelial bladder cancer (UBC) are frequently referred to as "disparate twins" despite their common tissue origin. They exhibit varying biological behaviors, prognostic outcomes, and responses to treatment. It is crucial to conduct dedicated clinical trials for UTUC as a separate entity rather than relying solely on UBC study results, giving that UTUC lags in evidence quantity and quality compared to UBC. Despite the superior outcomes of neoadjuvant treatment over adjuvant treatment in UBC trials, the currently available evidence for neoadjuvant therapy of UTUC remains limited in quantity and diversity, as the largest trial, POUT, is focused on adjuvant therapy. Additionally, the limited number of neoadjuvant trials for UTUC primarily utilize chemotherapy-based regimens, with little investigation into combination therapies. Of note, UTUC patients frequently have impaired renal functions, making a chemotherapy-independent approach a desirable alternative. On the other hand, given the short duration of neoadjuvant therapy, a combination therapy strategy appears to be necessary, especially with the increasing interest in immune therapy maintenance after surgery. Tislelizumab has demonstrated efficacy in patients with advanced or metastatic urothelial carcinoma. Disitamab Vedotin, a HER2-targeting antibody-drug conjugate (ADC), has demonstrated robust clinical efficacy in metastatic urothelial carcinoma patients with HER2 2+ or 3+ expression. Disitamab Vedotin in combination with PD-1 immunotherapy has shown remarkable results in locally advanced or metastatic urothelial carcinoma, regardless of HER2 expression, indicative of a synergistic effect between ADC and PD-1 immunotherapy. In this study, we aim to conduct a prospective phase II trial to investigate the efficacy and safety of neoadjuvant tislelizumab plus Disitamab Vedotin followed by adjuvant tislelizumab in patients with high-risk UTUC. **Methods:** This multi-center phase II trial aims to enroll 45 patients with histologically confirmed UTUC at clinical stage cT2-4N0M0 or cT1-4N1-2M0. Neoadjuvant therapy includes 4 cycles of Tislelizumab (200mg for each 3-week cycle) in combination with Disitamab Vedotin (2.0mg/kg for each 3-week cycle). Radical nephroureterectomy (including bladder cuff resection and regional lymph node dissection if indicated) will be performed if there is no obvious contraindication within 3-6 weeks after the final neoadjuvant therapy administration. Postoperative adjuvant treatment with 8 cycles of tislelizumab will be provided. The primary endpoint is pathological complete response rate. Secondary endpoints include overall survival, local recurrence free survival, distant metastasis free survival, FACT−G. Clinical trial information: ChiCTR2300067836. Research Sponsor: BeiGene, Ltd. & RemeGen, Ltd.

Pembrolizumab with favezelimab or vibostolimab for patients with bacillus Calmette-Guérin (BCG)–unresponsive high-risk (HR) non–muscle-invasive bladder cancer (NMIBC): Phase 2 KEYNOTE-057 cohort C.

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Background: In cohort A of the phase 2 KEYNOTE-057 study (NCT02625961), the PD-1 inhibitor pembrolizumab demonstrated antitumor activity (3-month complete response rate, 41%) in patients with BCG-unresponsive HR NMIBC with carcinoma in situ (CIS) ± papillary tumors who are ineligible for or declined radical cystectomy (RC). However, treatment combinations that improve outcomes and durability of response with pembrolizumab monotherapy are needed. Coinhibitory receptors LAG-3 and TIGIT contribute to immune tolerance in the tumor microenvironment, and co-blockade of PD-1 with LAG-3 or TIGIT has demonstrated antitumor activity in clinical studies. In cohort C of KEYNOTE-057, efficacy and safety of coformulations of pembrolizumab and the LAG-3 inhibitor favezelimab or the TIGIT inhibitor vibostolimab are being evaluated in patients with BCG-unresponsive HR NMIBC with CIS ± papillary tumors. **Methods:** Key eligibility criteria include adults with histologically confirmed HR NMIBC (CIS ± high-grade Ta or T1 at baseline) that is BCG-unresponsive (persistent or recurrent CIS ± Ta/T1 ≤12 month of completing adequate BCG therapy) who are ineligible for or declined RC and have an ECOG PS of 0-2. Enrollment is planned for 60 patients. Patients will be randomly assigned 1:1 to receive the coformulation of pembrolizumab 200 mg and vibostolimab 200 mg or the coformulation of pembrolizumab 200 mg and favezelimab 800 mg intravenously every 3 weeks for ≤35 cycles or until central pathology–confirmed ≥T1 at any time point, persistent or recurrent CIS or high-grade Ta at 24-week efficacy review or thereafter, unacceptable toxicity, patient or physician decision to withdraw, or administrative reasons to discontinue. Tumor assessment will be performed every 12 weeks for 2 years and every 24 weeks thereafter for up to 5 years. Primary end point is 12-month complete response rate of HR NMIBC by cystoscopy, cytology, biopsy, and radiologic imaging by central pathology and radiology review. Secondary end points include duration of response of HR NMIBC; overall complete response rate and complete response rates at 3 and 6 months; progression-free survival (PFS) to worsening of grade, stage, or death; PFS to muscle-invasive or metastatic disease or death; and overall survival. Efficacy will be evaluated in patients who receive ≥1 dose of treatment and have a baseline evaluation consisting of pre-enrollment cystoscopy, TURBT/biopsy, urine cytology, and baseline CTU imaging. Safety and tolerability will be evaluated in patients who receive ≥1 dose of treatment. Enrollment is ongoing in Asia, Australia, Europe, North America, and South America. Clinical trial information: NCT02625961. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Phase 3 KEYNOTE-992 study of pembrolizumab plus chemoradiotherapy versus placebo plus chemoradiotherapy in patients with muscle-invasive bladder cancer (MIBC).

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Background: Concurrent chemoradiotherapy (CRT) is a recommended treatment option for patients (pts) with MIBC who seek a bladder-preserving alternative to radical cystectomy and/or not candidates for radical cystectomy. The anti–PD-1 antibody pembrolizumab is approved for metastatic bladder cancer and non–muscle-invasive bladder cancer (NMIBC). The randomized, double-blind, phase 3 KEYNOTE-992 study (NCT04241185) is evaluating efficacy and safety of pembrolizumab plus CRT versus placebo plus CRT in pts with MIBC who chose bladder preservation. **Methods:** Eligibility criteria include adultswho have a histologically confirmed initial diagnosis of MIBC (T2-T4aN0M0) with ≥50% urothelial histology, ECOG PS score of 0 to 2, have received no prior therapy with anti–PD-1/L1 or agents directed to another stimulatory or coinhibitory T-cell receptor, and have planned treatment with one of the specified radiosensitizing chemotherapies. Prior treatment for NMIBC with intravesical instillation therapy such as BCG or intravesical chemotherapy is permitted. Approximately 636 pts will be randomly assigned 1:1 to receive pembrolizumab 400 mg IV or placebo IV every 6 weeks for up to 9 cycles, both with CRT. Investigator's choice of chemotherapy will be specified before random assignment. Pts will be stratified by ECOG PS (0 and 1 vs 2), PD-L1 combined positive score (<10 vs ≥10), T stage (T2 vs T3 and T4), and geographic region (United States vs European Union vs rest of the world). Radiosensitizing chemotherapy will be cisplatin monotherapy (35 mg/m^2 IV weekly on day 1), 5-fluorouracil (500 mg/m^2 on days 1-5 and days 22-26) plus mitomycin C (12 mg/m^2 on day 1), or gemcitabine monotherapy (27 mg/m^2 IV twice weekly on days 1 and 4). Radiation therapy will be conventional radiotherapy consisting of 64 Gy at 2 Gy/fraction over 6.5 weeks (whole bladder with or without pelvic nodes) or hypofractionated radiotherapy consisting of 55 Gy at 2.75 Gy/fraction over 4 weeks (whole bladder only). Imaging via CT and CT urography or magnetic resonance urography will be performed 10 weeks after completion of CRT, every 12 weeks until the end of year 2, then every 24 weeks thereafter. Adverse events (AEs) will be monitored throughout the study and up to 30 days after cessation of treatment (90 days for serious AEs). Primary end point is bladder-intact event-free survival (defined as time from random assignment to first documented occurrence of residual/recurrent MIBC, nodal or distant metastases, radical cystectomy, or death from any cause) as assessed by blinded independent central review and/or central pathology review. Secondary end points are overall survival, metastasis-free survival, time to cystectomy, time to occurrence of NMIBC, safety and tolerability, and patient-reported outcomes. Enrollment is ongoing in Asia, Australia, Europe, North America, and South America. Clinical trial information: NCT04241185. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Phase 3 KEYNOTE-676 cohort A: Bacillus Calmette-Guérin (BCG) with or without pembrolizumab for high-risk (HR) non–muscle-invasive bladder cancer (NMIBC) that persists/recurs after BCG induction.

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Background: Intravesical instillation of BCG is a standard-of-care treatment for patients with HR NMIBC, but up to 50% of patients later experience disease recurrence or progression to muscle-invasive bladder cancer (MIBC) despite BCG treatment. In the phase 2 KEYNOTE-057 study (NCT02625961), pembrolizumab monotherapy was shown to have antitumor activity in patients with HR BCG–unresponsive NMIBC who had carcinoma in situ (CIS) with or without papillary tumors and in patients with only papillary tumors. In cohort A of the randomized, phase 3 KEYNOTE-676 trial (NCT03711032), pembrolizumab plus BCG versus BCG alone is being evaluated in patients with persistent/recurrent HR NMIBC after first BCG induction. **Methods:** Key eligibility criteria include adults with histologically confirmed HR NMIBC (T1, high-grade Ta, and/or CIS) that is persistent/recurrent following 1 adequate course of BCG induction therapy, have no concurrent extravesical disease or history of extravesical disease that recurred within 2 years, have an ECOG PS score of 0 to 2, and have undergone cystoscopy/TURBT ≤12 weeks before randomization. Approximately 430 patients will be randomly assigned 1:1 to receive pembrolizumab 200 mg intravenously every 3 weeks plus BCG or BCG alone. BCG (50 mg) will be administered by intravesical instillation as induction therapy once weekly for 6 weeks and then as maintenance therapy once weekly for 3 weeks at weeks 13 and 25, then every 24 weeks (Q24W) thereafter. Treatment will continue for approximately 2 years (pembrolizumab) or 3 years (BCG), or until confirmed persistent/recurrent HR NMIBC or disease progression to MIBC or metastatic bladder cancer, unacceptable toxicity, or withdrawal. Randomization to treatment will be stratified by PD-L1 combined positive score (≥10 or <10), histology (CIS or non-CIS), and NMIBC disease history (persistence/recurrence 0 to ≤6 months or recurrence >6 to ≤12 months or recurrence >12 to ≤24 months). Response will be assessed by local cystoscopy and blinded independent central review of urine cytology and biopsy (as applicable) every 12 weeks for years 1 to 2 and Q24W for years 3 to 5. Computed tomography urography will occur every 72 weeks through year 5, then every 104 weeks thereafter. The primary end point is complete response rate in patients with CIS. Secondary end points are duration of response in patients with CIS, event-free survival, recurrence-free survival, time to cystectomy, overall survival, disease-specific survival, safety and tolerability, and patient-reported outcomes. Enrollment incohort A of KEYNOTE-676 is ongoing in Asia, Australia, Europe, and North America. Clinical trial information: NCT03711032. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS723 Trials in Progress Poster Session

Efficacy and safety of the combination of cisplatin plus nab-paclitaxel and nivolumab with radiotherapy after maximal tumor resection in non-metastatic muscle invasive bladder cancer (CNN-BC trial).

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Background: The therapeutic gold standard for muscle invasive bladder cancer (MIBC) is radical cystectomy (RC) preceded by neoadjuvant chemotherapy when appropriate. However, RC is a major surgery procedure with 13% rate of severe complication and a perioperative mortality rate of about 1.5 - 5 %. Trimodal therapy (TMT) is a "bladder sparing" option alternative to RC. TMT consists of complete transurethral bladder tumor resection (TURBT) followed by a combination of systemic chemotherapy and locoregional radiotherapy (RT), with the option of "salvage" cystectomy in case of local treatment failure. Immunotherapy with anti-PD1/PD-L1 monoclonal antibody significantly improves survival of metastatic BC patients, and it seems to potentiate the activity of RT without increased toxicity. Therefore, we investigate the role of a multimodal TMT strategy to increase the disease-free survival (DFS) and avoid or delay RC in non-metastatic MIBC pts. **Methods:** CNN-BC trial (NCT05203913) is a phase 2, open-label, mono-institutional study evaluating the activity and safety of TMT with cisplatin, nab-paclitaxel and nivolumab as systemic therapy in non-metastatic MIBC pts. Eligible pts should have undergone complete TURBT with diagnosis of T2-T3 N0M0 urothelial carcinoma, and no evidence of lymph nodes or metastatic disease at FDG-PET within 6 weeks from the start of treatments. TMT consists of nivolumab (480 mg IV every 4 weeks for a total of 13 doses), weekly nab-paclitaxel (60mg/m2) plus cisplatin (20mg/m2) administered concurrently with RT (60Gy in 25 fractions over 5 weeks on original bladder tumor, plus a concomitant boost of 50Gy in 25 fractions on whole bladder and pelvic nodes). The primary endpoint is the 1-year DFS rate, defined as the rate of survival free of recurrence in pelvic nodes or bladder, or appearance of distant metastases. Secondary endpoints include: the rate of pts who require salvage cystectomy, the rate of locoregional complete response (CR) and of locoregional DFS, median DFS, safety, and quality of life. Exploratory biomarkers analysis will be performed. The trial is actively recruiting. Clinical trial information: NCT05203913. Research Sponsor: BMS.