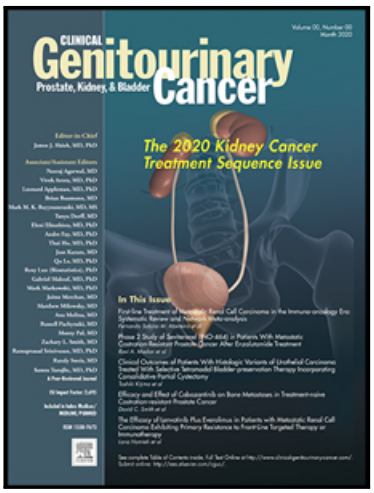

Treatment rechallenge with immune checkpoint inhibitors in advanced urothelial carcinoma

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Key take home messages:

- Patients with advanced urothelial cancer (aUC) rechallenged with an ICI-based regimen may achieve disease control
- Rechallenge with ICI-based therapy in aUC seems feasible with manageable toxicity
- Further data are needed to optimally select patients for ICI rechallenge in aUC

Treatment rechallenge with immune checkpoint inhibitors in advanced urothelial carcinoma

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Abstract (Word count: 252**):**

Objectives: To examine patient and disease characteristics, toxicity, and clinical outcomes for patients with advanced urothelial carcinoma (aUC) who are rechallenged with immune checkpoint inhibitor (ICI)-based therapy.

Patients and Methods: In this retrospective cohort, we included patients treated with ICI for aUC after having prior ICI treatment. Endpoints included the evaluation of radiographic response and disease control rates with 1st and 2nd ICI courses, outcomes based on whether there was a change in ICI class (anti-PD-1 vs anti-PD-L1), and assessment of the reasons for ICI discontinuation.

Results: We identified 25 patients with aUC from nine institutions who received two separate ICI courses. ORR with 1st ICI and 2nd ICI were 39% and 13%, respectively. Most patients discontinued 1st ICI due to progression (n=19) or treatment-related toxicity (n=4). Thirteen patients received non-ICI treatment between the 1st and 2nd ICI, and 12 patients changed ICI class (anti-PD-1 vs anti-PD-L1) at rechallenge. Among 10 patients who changed ICI class, eight (80%) had progressive disease as best response with 2nd ICI, while among 12 patients re-treated with the same ICI class, only three (25%) had progressive disease as best response at the time of rechallenge. With 2nd ICI, most patients discontinued treatment due to progression (n=18) or patient preference (n=2).

Conclusions: A proportion of patients with aUC, rechallenged with ICI-based regimen may achieve disease control, supporting clinical trials in that setting, especially with ICI-based combinations. Future studies are needed to validate our results and should also focus on identifying biomarkers predictive of benefit with ICI rechallenge.

MicroAbstract

Immune checkpoint inhibitors (ICI) improve outcomes in patients with advanced urothelial carcinoma (aUC). However, most patients may not respond and develop progressive disease, while toxicity can be an issue. ICI therapy remains a questionable consideration for rechallenge after other therapies are used. Our study described characteristics and treatment response in patients with aUC who were rechallenged with an ICI-based regimen.

Keywords

Bladder cancer, immune checkpoint inhibitor, immunotherapy, urinary tract cancer, urothelial carcinoma

Abbreviations:

aUC: Advanced urothelial carcinoma
ADC: Antibody-drug conjugate
BCG: Bacille Calmette-Guérin
CR: Complete response
EV: Enfortumab vedotin
FDA: Food and drug administration
FGFR: Fibroblast growth factor receptors
ICIs: immune checkpoint inhibitors
IRAEs: Immune-related adverse events
MIBC: Muscle invasive bladder cancer
NSCLC: Non-small cell lung cancer
ORR: Overall response rate
OS: Overall survival
PD1: Programmed cell death protein 1
PDL1: Programmed cell death ligand-1
PR: Partial response
SD: Stable disease
SG: Sacituzumab govitecan
TRAEs: Treatment related adverse events

Introduction

In recent years, the introduction of immune checkpoint inhibitors (ICIs) has revolutionized the therapeutic landscape of advanced urothelial carcinoma (aUC). Pembrolizumab and atezolizumab were FDA-approved for use in the frontline setting in the US (for cisplatin-ineligible patients with PD-L1 high

tumors [Atezolizumab] or for platinum-ineligible patients [atezolizumab and pembrolizumab]), while pembrolizumab, nivolumab and avelumab were FDA-approved in the platinum-refractory setting.(1-4) Avelumab was also FDA-approved as switch-maintenance therapy in patients with clinical benefit (response or stable disease) with frontline platinum-based chemotherapy.(5) Atezolizumab and durvalumab demonstrated efficacy in the platinum-refractory setting,(6, 7) but their platinum-refractory FDA label were subsequently voluntarily withdrawn due to negative phase III trials.(8) ICIs have also been introduced as treatment for earlier stages of urothelial carcinoma. Nivolumab was FDA-approved as adjuvant therapy for muscle invasive urothelial cancer (MIUC) based on the results of the Checkmate-274 trial(9) and pembrolizumab was approved for BCG-unresponsive high-risk non-muscle invasive bladder cancer (NMIBC) with carcinoma *in situ* in patients who refuse or are unfit for radical cystectomy based on the Keynote-057 trial.(10) Other ICIs have also been investigated as neoadjuvant and/or adjuvant treatment in several clinical trials. This expansion of ICI use in earlier disease settings suggests clinical scenarios where patients previously treated with ICI may be considered for repeat ICI treatment in a later treatment setting, either as a single agent in an approved indication or in potential combinations in clinical trials.

Despite the improvement in outcomes for a subset of patients treated with ICI, most patients with aUC are not cured by this therapy and most inevitably progress. Upon progression on these agents, patients have other therapeutic options, including enfortumab vedotin (EV),(11) sacituzumab govitecan (SG),(12) erdafitinib (for the proportion of patients with FGFR2 or FGFR3 activating mutation or fusion) and salvage chemotherapy. (13) However, upon exhaustion of these options, ICI remains a questionable consideration for rechallenge given the favorable toxicity profile. Prior studies have suggested that therapeutic rechallenge with ICI, defined as reintroduction of ICI as either monotherapy or combination treatment after a prior course of ICI treatment, may still result in clinical benefit in various tumors, such as melanoma(14), non-small cell lung cancer (NSCLC)(15), renal cell carcinoma(16, 17) (and two ongoing trials; NCT04987203, NCT04338269) and urothelial carcinoma(18, 19). Given the increased use of ICI regimens in the adjuvant and NMIBC setting, this clinical scenario in aUC will only continue to increase in relevance. Therefore, generating data applicable to these clinical settings can help inform the literature and future clinical trial designs. In this retrospective multi-institutional cohort study, we describe the characteristics and treatment response for patients with aUC who received ICI-based therapy with two distinct ICI-courses during their treatment.

Patients and Methods

Patient selection and data collection:

We undertook this retrospective cohort study after obtaining approval by institutional review board and in concordance with the Declaration of Helsinki. Patients who met inclusion criteria were identified from a larger cohort of patients with a diagnosis of aUC treated with ICI(20-26). Patients in the cohort were identified using a combination of provider-driven and electronic health record search algorithms. For this study, we aimed to include patients treated with ICI for aUC after having had prior treatment with ICI in either the advanced or the localized disease setting. Patients were excluded if they received only one ICI-based regimen or ICI for a different indication other than UC. For data collection and storage, we used web-based, secure and standardized REDCap capture tools hosted at the Institute of Translational Sciences(27, 28). Data collected included patient demographics, cancer histology type, laboratory values, sites of metastatic disease and outcomes (e.g. response, progression), specific ICI used in each treatment setting, reasons for ICI discontinuation and other treatments administered between the ICI regimens. Pathology and radiology results were assessed based on notes in the electronic health record; no central review of either was performed. All patients underwent imaging at the discretion of treating provider as per local practice.

Statistical Analysis

Baseline characteristics were summarized using descriptive statistics and compared via chi-squared and paired t-test, for categorical and continuous variables, respectively and Wilcoxon signed-rank test for non-parametric data. The main endpoints were overall response rate (ORR) by radiological evaluation at nonspecific time points [ORR: complete or partial response (CR, PR)], as well as disease control rate, comprised of CR, PR or stable disease (SD) with 1st and 2nd ICI, respectively. We calculated ORR and

disease control rate excluding the two patients who received 2nd line combination treatment with EV and pembrolizumab. Moreover, we evaluated response to the 2nd ICI based on response to the 1st ICI, response to 2nd ICI based on the time from 1st ICI initiation to 2nd ICI initiation, and response to 2nd ICI based on whether ICI class stayed the same or changed between the two ICI courses from anti-PD-1 to anti-PD-L1 or *vice versa*. We also assessed the reasons for ICI discontinuation, as well as the number and type of treatments administered between 1st and 2nd ICI-based course. Response was determined by the chart abstractor based on best available information in notes and radiographic studies. All analyses were performed with R version 4.1.0 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

We identified 25 patients with aUC across nine institutions in the United States and Europe who received two separate ICI-based regimens throughout their treatment course between 2013 and 2021. Demographic information can be found in **Supplementary Table 1**. Most patients were men (84%), White (80%), had pure urothelial histology (72%), and their primary tumor was in the bladder (68%). Most patients received anti-PD1 or anti-PDL1 agent as monotherapy, but a subset (n = 1 for 1st ICI and n=2 for 2nd ICI) received combination treatments. One patient was treated with durvalumab and tremelimumab combination as their 1st ICI regimen and later received pembrolizumab and EV combination during rechallenge, another patient received the combination of pembrolizumab with EV at the time of ICI rechallenge.

Baseline disease features and laboratory findings were overall similar at the time of 1st ICI and 2nd ICI-based course. However, patients receiving a 2nd ICI had higher disease burden with more metastatic sites involved. Overall, 39% of patients demonstrated response (CR or PR) to 1st ICI administration and 13% had response at the time of rechallenge to ICI monotherapy (n=23 patients) as shown in **Table 1**. Two additional patients received combination of EV and pembrolizumab at the time of rechallenge. Both patients had PD as best response to the 1st ICI. At the time of rechallenge one patient had PD and the other one had CR. Excluding the two cases that received combination EV and pembrolizumab as 2nd line ICI (ID 16 and 17), the percentage of patients demonstrating progression as best response between 1st and 2nd ICI course, was 39% and 47% accordingly. Among the nine patients who responded to 1st ICI, two patients had PR and two had SD (44% disease control rate) with ICI rechallenge. Among the four patients who had stable disease as best response to the 1st ICI, two (50%) had disease control (1SD and 1PR) and two (50%) had PD. On the other hand, among 9 patients who had progressive disease as best response to 1st ICI, four (44%) had disease control (4 SD) at the time of rechallenge with 2nd ICI. (**Table 2**).

Thirteen patients received at least one other (non-ICI) line of treatment between the 1st and the 2nd ICI with the majority (9 of 13) receiving platinum-based chemotherapy (**Table 3**). Twelve patients changed ICI class during rechallenge. Excluding patients that received the combination of EV and pembrolizumab as ICI rechallenge (n=2), two (20%) demonstrated disease control during treatment with 2nd ICI. On the other hand, among 12 patients re-treated with the same class of ICI, eight (66%) had disease control at rechallenge. One patient received a second ICI in a clinical trial (tremelimumab, which constitutes an anti-CTLA-4 agent). Most patients (21/25, 84%) were rechallenged with a different ICI than the one initially administered. Four patients (16%) were rechallenged using the same ICI after a minimum of 36 weeks between the initiation of the two regimens; of those, two patients had stable disease, while one patient each demonstrated partial response and progressive disease with ICI rechallenge, respectively (Table 3).

When assessing reasons for discontinuing ICI-based treatment, we found that among 23 patients who discontinued therapy with the 1st ICI, 19 (82%) had radiographic or clinical progression, while four patients (17%) stopped due to treatment-related toxicity. Of those 19 who discontinued 1L ICI due to progression, five patients had stable disease, one patient had partial response and another patient complete response as the best response to 2nd ICI, however the latter patient received combination EV and pembrolizumab. Of those four patients who stopped 1st ICI due to treatment-related toxicity, two patients had partial response and two patients had stable disease as best response with the 2nd ICI. None of the patients with treatment-related toxicity to 1st ICI had recurrence of the same toxicity with 2nd ICI. Regarding 2nd ICI-based course, no patient discontinued treatment due to toxicity and the most common

reasons for discontinuation was clinical/radiographic progression (n=18) (Table 3**).** Two patients completed the intended course of therapy with the 1st ICI, while for 2nd ICI regimen, only one patient completed the intended course as per the local provider's description.

Among the 25 patients, 9 patients received interim platinum-based chemotherapy between the 1st and 2nd ICI. Two patients (ID 15 and 20) received first line ICI on a clinical trial, two patients (ID 5 and 6) received first line ICI because of recurrence within 12 months of receiving perioperative platinum-based chemotherapy for muscle invasive bladder cancer, and the other 5 patients (ID 1, 13, 17, 18 and 24) received first line platinum-based chemotherapy, followed by ICI but then were re-trialed with platinum-based chemotherapy prior to rechallenge with 2nd ICI.

Discussion

In this multi-institutional retrospective case series, we assessed 25 patients with aUC who were rechallenged with the same or, much more commonly, another ICI-based treatment. The results suggest that about half of the patients who were rechallenged with an ICI-based regimen achieved disease control. Our data have clinical relevance, since to date, there has been no indication or approval to use ICI in a patient with UC and progression on a prior ICI, and such patients were excluded from ICI-based therapies in clinical trials. As ICIs are increasingly introduced in earlier disease states and treatment settings and patients with aUC may have longer survival in the context of novel therapies, a population of patients previously exposed to an ICI who may receive a new ICI-based course may become more common.

The introduction of new therapeutic agents, such as antibody-drug conjugates (ADC) EV and SG, as well as erdafitinib in selected patients, provides more options for patients with aUC.(11, 12) ICI rechallenge could be a potential consideration for patients who progressed, were not ideal candidates or interrupted ICI due to immune related adverse event (IRAE) that has then became well controlled. Reintroduction of ICI may also have a role as part of treatment combinations. Currently ongoing clinical trials are investigating combinations of ICI with ADC and other targeted agents, such as EV, SG and FGFR inhibitors(29). Combination therapy of EV with pembrolizumab was granted breakthrough therapy designation by the FDA based on the results of Cohort A from EV-103 trial, which showed an impressive ORR of 73% (CR 18%), 93% disease control rate and 56% overall survival (OS) rate at two years among cisplatin-ineligible patients treated in the 1st line setting.(30) An impressive ORR 64.5% with pembrolizumab/EV combination (median response duration not reached) was demonstrated in a larger randomized cohort K of the same trial that was recently presented at the 2022 annual ESMO meeting (31). Cohort 3 of the TROPHY-U-01 trial also investigated the efficacy of SG and pembrolizumab combination as second line therapy in patients with platinum-refractory aUC, demonstrating ORR 34% and disease control rate 61%.(32) These data with ICI-based combinations look promising overall and raise the question of whether ICI rechallenge may be attempted in a proportion of patients (e.g. NCT03606174). EV has been shown to be immunogenic in promoting recruitment and activation of immune cells(33). In our cohort, two patients received 2nd ICI combined with EV, with one patient demonstrating a complete response. This may suggest a potential future treatment strategy for ICI rechallenge that should be evaluated in larger prospective cohorts and clinical trials. The lack of biomarkers predictive of response and well-established criteria of candidacy for ICI rechallenge remain major limitations of this approach, while concerns also exist over the risk of IRAE.

Rechallenge with ICIs in patients with cancer could raise concerns among clinicians regarding the risk of IRAE, especially among patients with history of IRAEs with 1st ICI administration. The results of our cohort, in which none of the patients on 2nd ICI discontinued treatment due to adverse events, are in support of prior literature suggesting that ICI rechallenge can be tolerable.(34) However, only a minority of the patients in our cohort discontinued first ICI therapy due to IRAE and the details of the type, grade and extent of IRAE were not investigated in detail. These IRAE-related details can be very important when considering ICI rechallenge. Further, these results should be considered in the context of potentially greater motivation of patients with aUC to consider ICI rechallenge given the relatively limited therapeutic options. Prior literature additionally suggests potentially improved response rates (35) and survival (36) in patients with IRAEs in the context of ICI therapy. The results from our cohort seem consistent with this hypothesis, as all the patients (n=4) who discontinued 1st ICI due to treatment-related

toxicity had disease control at rechallenge however, additional data are needed to answer this question more definitively.

As discussed earlier, rechallenge with ICIs in aUC is currently a non-standard treatment approach that is used very infrequently. Consequently, it is important to consider the specific clinical context in which this approach can best be utilized. In our cohort, ORR was lower with 2nd ICI-based course as opposed to the 1st course, which may have been confounded by the increased cancer burden and potential emergence of more aggressive and treatment-refractory disease in the context of prior ICI exposure and other therapies. The timing of rechallenge in relation to the prior ICI-based therapy course is of interest as a potential prognostic or predictive biomarker of response. Our results may suggest that patients more likely to benefit from ICI rechallenge were those with a greater time interval between the initiation of 1st ICI and time of rechallenge although these findings are limited and warrant validation in larger prospective cohorts and clinical trials.

In our cohort, most patients received rechallenge with a different ICI than the one used during the 1st course, and about half of patients were rechallenged with a drug with a similar mechanism of action (anti-PD1 after anti-PD1, or anti-PDL1 after anti-PDL1). Little is currently known about any difference in response and outcomes between anti-PD1 and anti-PDL1 agents in the absence of direct comparison in a clinical trial: while both classes inhibit the same signaling pathway, a number of datasets might suggest potential differences.(3, 37-39) The fact that fewer patients that changed ICI class demonstrated disease control as opposed to those that remained on treatment with the same class raises the question about switching ICI class. However, the sample size is too small to draw definitive conclusions and only generate a hypothesis that can be further assessed in larger cohorts.

Limitations of our study include: a retrospective design that lacks randomization, potential selection bias, and residual confounding factors. Based on that, we could not assess the efficacy of the second ICI course vs other therapies, while the tumor biology may have impacted outcomes. In addition, clinical practices, surveillance protocols, and follow-up timelines may vary across the participating institutions, while differences in documentation might exist. Centralized review of pathology or imaging was not applied, but all participating sites are academic sites with expert genitourinary oncologists, radiologists, and pathologists. Response and progression were determined by systematic comprehensive chart review based on clinical and radiology notes without mandating formal, prespecified interval assessments via RECIST 1.1 criteria. Moreover, we did not have patients who received ICI for localized UC to inform clinical discussions regarding the use of ICI for aUC in the context of prior pembrolizumab for high-risk BCG-unresponsive carcinoma *in situ* or prior nivolumab as adjuvant therapy in MIUC. With the increasing use of those therapies, future cohort studies may include those patients. Moreover, due to the low sample size, it was hard to assess in detail the exact role of the systemic therapies used in-between ICI-based regimens, and the role of clinical benefit and duration of the 1st ICI course.

Despite the limitations, to our knowledge, this is the largest retrospective cohort of patients with aUC who received ICI rechallenge. Results are hypothesis-generating and can be of value for clinicians and patients facing limited treatment options and contemplating reintroducing ICI in the care of patients with aUC. ICI rechallenge remains a non-standard practice for aUC and while the available literature on rechallenge efficacy and safety is scarce, the results from this cohort provide useful information on a subject that has not been adequately studied in clinical trials. Based on our results, rechallenge with ICI-based therapy in aUC may be effective and well-tolerated in several patients, but further data are needed to optimally select patients for this approach.

Author Contributions

Dimitrios Makrakis MD, Dimitra Rafailia Bakaloudi MD, Rafee Talukder MD: Conceptualization, Methodology, Formal analysis, Investigation, Data Curation, Writing- Original Draft, Writing-Review and Editing. **Genevieve Ihsiu Lin:** Statistical Analysis**, Leonidas N. Diamantopoulos MD**: Investigation, Data Curation, Writing- Review and Editing. **Tanya Jindal BS, BA**: Investigation, Writing- Review and Editing. **Naomi Vather-Wu**: Investigation, Writing- Review and Editing. **Yousef**

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Clinical Practice Points

- While immune checkpoint inhibitors (ICI) improve outcomes in a significant number of patients with advanced urothelial Ca (aUC), most patients do not have tumor response and almost all eventually have progressive disease; immune related adverse events might also cause morbidity and mortality.
- ICI therapy remains a questionable consideration for rechallenge given the favorable toxicity profile, esp. after the exhaustion of other therapies.
- In this study, we describe in detail the demographics, disease characteristics, treatment patterns and response in patients with aUC who received two distinct ICI-based therapy courses
- About half of the patients with aUC rechallenged with an ICI-based regimen achieved disease control (no progression as best response)
- Rechallenge with ICI-based therapy in aUC seems feasible with manageable toxicity but further research is needed to assess that treatment strategy

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Conflicts of Interest

Dimitrios Makrakis, Dimitra Rafailia Bakaloudi, Rafee Talukder, Genevieve Ihsiu Lin, Leonidas N. Diamantopoulos, Tanya Jindal, Naomi Vather-Wu, Nishita Tripathi, Eric Lu, Claudia-Maria Fulgenzi: No conflicts to disclosure

Yousef Zakharia: Advisory Board: Bristol Myers Squibb, Amgen, Roche Diagnostics, Novartis, Janssen, Eisai, Exelixis, Castle Bioscience, Genzyme Corporation, Astrazeneca, Array, Bayer, Pfizer, Clovis, EMD serono, Myovant. Grant/research support from: Institution clinical trial support from NewLink Genetics, Pfizer, Exelixis, Eisai. DSMC: Janssen Research and Development Consultant honorarium: Pfizer, Novartis

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References

1. Balar AV, Castellano D, O'Donnell PH, Grivas P, Vuky J, Powles T, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. The Lancet Oncology. 2017;18(11):1483-92.
2. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med. 2017;376(11):1015-26.
3. Gopalakrishnan D, Koshkin VS, Ornstein MC, Papatsoris A, Grivas P. Immune checkpoint inhibitors in urothelial cancer: recent updates and future outlook. Therapeutics and clinical risk management. 2018;14:1019-40.

4. Sharma P, Retz M, Siefker-Radtke A, Baron A, Necchi A, Bedke J, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. The Lancet Oncology. 2017;18(3):312-22.
5. Powles T, Park SH, Voog E, Caserta C, Valderrama BP, Gurney H, et al. Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma. The New England journal of medicine. 2020;383(13):1218-30.
6. Powles T, O'Donnell PH, Massard C, Arkenau HT, Friedlander TW, Hoimes CJ, et al. Efficacy and Safety of Durvalumab in Locally Advanced or Metastatic Urothelial Carcinoma: Updated Results From a Phase 1/2 Open-label Study. JAMA oncology. 2017;3(9):e172411.
7. Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet (London, England). 2017;389(10064):67-76.
8. Powles T, Durán I, van der Heijden MS, Loriot Y, Vogelzang NJ, De Giorgi U, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet (London, England). 2018;391(10122):748-57.
9. Bajorin DF, Witjes JA, Gschwend JE, Schenker M, Valderrama BP, Tomita Y, et al. Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. New England Journal of Medicine. 2021;384(22):2102-14.
10. Balar AV, Kamat AM, Kulkarni GS, Uchio EM, Boormans JL, Roumiguié M, et al. Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study. The Lancet Oncology. 2021;22(7):919-30.
11. Powles T, Rosenberg JE, Sonpavde GP, Loriot Y, Durán I, Lee J-L, et al. Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma. New England Journal of Medicine. 2021;384(12):1125-35.
12. Tagawa ST, Balar AV, Petrylak DP, Kalebasty AR, Loriot Y, Fléchon A, et al. TROPHY-U-01: A Phase II Open-Label Study of Sacituzumab Govitecan in Patients With Metastatic Urothelial Carcinoma Progressing After Platinum-Based Chemotherapy and Checkpoint Inhibitors. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2021;39(22):2474-85.
13. Loriot Y, Necchi A, Park SH, Garcia-Donas J, Huddart R, Burgess E, et al. Erdafitinib in Locally Advanced or Metastatic Urothelial Carcinoma. New England Journal of Medicine. 2019;381(4):338-48.
14. Zaremba A, Eggermont AMM, Robert C, Dummer R, Ugurel S, Livingstone E, et al. The concepts of rechallenge and retreatment with immune checkpoint blockade in melanoma patients. European journal of cancer (Oxford, England : 1990). 2021;155:268-80.
15. Xu Z, Hao X, Yang K, Wang Q, Wang J, Lin L, et al. Immune checkpoint inhibitor rechallenge in advanced or metastatic non-small cell lung cancer: a retrospective cohort study. Journal of cancer research and clinical oncology. 2022.
16. Vauchier C, Auclin E, Barthelemy P, Carril L, Ryckewaert T, Borchiellini D, et al. Rechallenge of nivolumab in metastatic renal cell carcinoma, an ambispective multicenter study (RENIVO). Journal of Clinical Oncology. 2021;39(6_suppl):330-.
17. Killock D. ICI rechallenge in mRCC. Nature Reviews Clinical Oncology. 2020;17(9):520-.
18. Bimbatti D, Maruzzo M, Pierantoni F, Diminutto A, Dionese M, Deppieri FM, et al. Immune checkpoint inhibitors rechallenge in urological tumors: An extensive review of the literature. Critical reviews in oncology/hematology. 2022;170:103579.

19. Jindal T, Chou J, Friedlander T, Barata PC, Koshkin VS. Repeat Treatment of Patients With Advanced Urothelial Carcinoma With Immune Checkpoint Inhibitors Following Prior Progression on a Checkpoint Inhibitor Regimen: A Case Series. Clinical genitourinary cancer. 2022;20(2):189-94.
20. Khaki AR, Li A, Diamantopoulos LN, Miller NJ, Carril-Ajuria L, Castellano D, et al. A New Prognostic Model in Patients with Advanced Urothelial Carcinoma Treated with First-line Immune Checkpoint Inhibitors. European urology oncology. 2021;4(3):464-72.
21. Makrakis D, Talukder R, Diamantopoulos LN, Carril-Ajuria L, Castellano D, De Kouchkovsky I, et al. Association of prior local therapy and outcomes with programmed-death ligand-1 inhibitors in advanced urothelial cancer. BJU international. 2022;130(5):592-603.
22. Makrakis D, Talukder R, Lin GI, Diamantopoulos LN, Dawsey S, Gupta S, et al. Association Between Sites of Metastasis and Outcomes With Immune Checkpoint Inhibitors in Advanced Urothelial Carcinoma. Clinical genitourinary cancer. 2022;20(5):e440-e52.
23. Talukder R, Makrakis D, Lin GI, Diamantopoulos LN, Dawsey S, Gupta S, et al. Association of the Time to Immune Checkpoint Inhibitor (ICI) Initiation and Outcomes With Second Line ICI in Patients With Advanced Urothelial Carcinoma. Clinical genitourinary cancer. 2022.
24. Talukder R, Makrakis D, Diamantopoulos LN, Carril-Ajuria L, Castellano D, De Kouchkovsky I, et al. Response and Outcomes to Immune Checkpoint Inhibitors in Advanced Urothelial Cancer Based on Prior Intravesical Bacillus Calmette-Guerin. Clinical genitourinary cancer. 2022;20(2):165-75.
25. Esagian SM, Khaki AR, Diamantopoulos LN, Carril-Ajuria L, Castellano D, De Kouchkovsky I, et al. Immune checkpoint inhibitors in advanced upper and lower tract urothelial carcinoma: a comparison of outcomes. BJU international. 2021;128(2):196-205.
26. Khaki AR, Li A, Diamantopoulos LN, Bilen MA, Santos V, Esther J, et al. Impact of performance status on treatment outcomes: A real-world study of advanced urothelial cancer treated with immune checkpoint inhibitors. Cancer. 2020;126(6):1208-16.
27. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. Journal of biomedical informatics. 2019;95:103208.
28. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. Journal of biomedical informatics. 2009;42(2):377-81.
29. Feng Z, Vuky J. Combination Therapy With Immune Checkpoint Inhibitors in Urothelial Carcinoma: Current Data and Future Outlook. Oncology (Williston Park, NY). 2021;35(7):410-20.
30. Hoimes CJ, Flaig TW, Milowsky MI, Friedlander TW, Bilen MA, Gupta S, et al. Enfortumab Vedotin Plus Pembrolizumab in Previously Untreated Advanced Urothelial Cancer. J Clin Oncol. 2022:101200jco2201643.
31. Rosenberg J.E. MM, Ramamurthy C., Mar N., et al. Study EV-103 Cohort K: Antitumor activity of enfortumab vedotin (EV) monotherapy or in combination with pembrolizumab (P) in previously untreated cisplatin-ineligible patients (pts) with locally advanced or metastatic urothelial cancer (la/mUC). Annals of Oncology. 2022:S808-S69.
32. Grivas P, Pouessel D, Park CH, Barthélémy P, Bupathi M, Petrylak DP, et al. TROPHY-U-01 Cohort 3: Sacituzumab govitecan (SG) in combination with pembrolizumab (Pembro) in patients (pts) with metastatic urothelial cancer (mUC) who progressed after platinum (PLT)-based regimens. Journal of Clinical Oncology. 2022;40(6_suppl):434-.
33. Liu BA, Olson D, Snead K, Gosink J, Tenn E-M, Zaval M, et al. Abstract 5581: Enfortumab vedotin, an anti-Nectin-4 ADC demonstrates bystander cell killing and immunogenic cell death

anti-tumor activity mechanisms of action in urothelial cancers. Cancer Research. 2020;80(16_Supplement):5581-.
34. Plazy C, Hannani D, Gobbini E. Immune Checkpoint Inhibitor Rechallenge and Resumption: a Systematic Review. Current oncology reports. 2022.
35. Inno A, Roviello G, Ghidini A, Luciani A, Catalano M, Gori S, et al. Rechallenge of immune checkpoint inhibitors: A systematic review and meta-analysis. Critical reviews in oncology/hematology. 2021;165:103434.
36. Albandar HJ, Fuqua J, Albandar JM, Safi S, Merrill SA, Ma PC. Immune-Related Adverse Events (irAE) in Cancer Immune Checkpoint Inhibitors (ICI) and Survival Outcomes Correlation: To Rechallenge or Not? Cancers. 2021;13(5).
37. De Sousa Linhares A, Battin C, Jutz S, Leitner J, Hafner C, Tobias J, et al. Therapeutic PD-L1 antibodies are more effective than PD-1 antibodies in blocking PD-1/PD-L1 signaling. Scientific Reports. 2019;9(1):11472.
38. Sonpavde GP, Grivas P, Lin Y, Hennessy D, Hunt JD. Immune-related adverse events with PD-1 versus PD-L1 inhibitors: a meta-analysis of 8730 patients from clinical trials. Future oncology (London, England). 2021;17(19):2545-58.
39. Tzeng A, Diaz-Montero CM, Rayman PA, Kim JS, Pavicic PG, Jr., Finke JH, et al. Immunological Correlates of Response to Immune Checkpoint Inhibitors in Metastatic Urothelial Carcinoma. Targeted oncology. 2018;13(5):599-609.

Table 1: Disease characteristics and responses to 1st and 2nd ICIs

	1st ICI	**2nd ICI**	**P-value***
ECOG PS			
0	17 (68%)	11 (44%)	0.379
1	4 (16%)	7 (28%)	
2	1 (4%)	3 (12 %)	
3	1 (4%)	1 (4%)	
Missing	2 (8%)	3 (12%)	
Metastatic sites (n)			
0	2 (8%)	0 (0%)	0.059
1	14 (56%)	9 (36%)	
2	8 (32%)	8 (32%)	
3	0 (0%)	5 (20%)	
4	1 (4%)	3 (12%)	
Metastatic sites (type)			
Lymph node	15 (60%)	19 (76%)	0.513
Soft tissue	3 (12%)	5 (20%)	
Local recurrence (bladder, ureter, kidney)	2 (8%)	2 (8%)	
Bone	1 (4%)	6 (24%)	
Lung	7 (28%)	12 (48%)	
Liver	4 (16%)	5 (20%)	
Bowel	0 (0%)	1 (4%)	

Brain/CNS	0 (0%)	1 (4%)	
Adrenal	0 (0%)	1 (4%)	
Peritoneum	1 (4%)	0 (0%)	
Uterus	1 (4%)	0 (0%)	
GFR (ml/min per 1.73m^2)			
Mean (SD)	58 (18.10)	65 (14.30)	0.154
Missing	1 (4%)	2 (8%)	
Albumin (g/dL)			
Mean (SD)	3.8 (0.49)	3.7 (0.60)	0.369
Missing	2 (8%)	5 (20%)	
Hemoglobin (g/dL)			
Mean (SD)	12.5 (1.9)	11.7 (2.2)	0.327
Missing	0 (0%)	4 (16%)	
Absolute lymphocyte count (x10^3/uL)			
Mean (SD)	1.7 (0.6)	1.2 (0.6)	0.298
Median [Min, Max]	1.70 [0.5, 2.8]	1.2 [0.3, 2.7]	
Missing	2 (8%)	6 (24%)	
Absolute neutrophil count (x10^3/uL)			
Mean (SD)	5.53 (4.8)	5.36 (3.82)	0.601
Median [Min, Max]	4.45 [1.4, 23.8]	4.2 [1.4, 15.5]	
Missing	1 (4%)	4 (16%)	

*Chi-squared and paired t-test used for categorical and continuous variables respectively and Wilcoxon Signed Rank test for non-parametric data (PS: performance status)

Table 2: Treatment response and average time of treatment initiation between 1st and 2nd ICI

	n (%)	**Weeks, median (min, max)**
Best Response to 1st ICI		
CR+PR	9 (36%)	
Complete response	3 (12%)	
Partial response	6 (24%)	
Stable disease	4 (16%)	
Progressive disease	11 (44%)	
Unknown	1 (4%)	
Best Response to 2nd ICI		
CR+PR	4 (16%)	103.6 [17, 155]

Complete response	1 (4%)	17.0
Partial response	3 (12%)	134.0 [73, 155]
Stable disease	8 (32%)	45.0 [10, 180]
Progressive disease	12 (48%)	43.5 [22, 189]
Unknown	1 (4%)	
CR: Complete Response, PR: Partial Response		

* One patient missing response data

Table 3: Treatment characteristics

	1st ICI			2nd ICI			Between 1st and 2nd ICI		
ID	**ICI used**	**Best response**	**Reason for discontinuation**	**ICI used**	**Best response**	**Reason for discontinuation**	**Weeks**	**1st interim therapy**	**2nd interim therapy**
1	Nivolumab	Partial response	radiographic progression	Pembrolizumab	Progressive disease	radiographic progression	189	Platinum-Cisplatin	
2	Atezolizumab	Partial response	radiographic progression	Pembrolizumab	Progressive disease	clinical progression	147		
3	Nivolumab	Progressive disease	radiographic progression	Pembrolizumab	Unknown	clinical progression	8		
4	Pembrolizumab	Complete response	radiographic progression	Tremelimumab	Stable disease	radiographic progression	29		
5	Nivolumab	Stable disease	clinical progression	Pembrolizumab	Stable disease	Death from other causes	93	Platinum-Cisplatin	

6	Durvalumab	Partial response	radiographic progression	Pembrolizumab	Progressive disease	clinical progression	100	Platinum-Cisplatin	
7	Nivolumab	Progressive disease	radiographic progression	Nivolumab	Stable disease	patient preference	208		
8	Nivolumab	Progressive disease	radiographic progression	Atezolizumab	Progressive disease	radiographic progression	40		
9	Nivolumab	Partial response	radiographic progression	Pembrolizumab	Partial response	Unknown if was stopped	134	Taxane	
10	Pembrolizumab	Progressive disease	radiographic progression	Pembrolizumab	Progressive disease	radiographic progression	36	Taxane	
11	Pembrolizumab	Progressive disease	treatment related toxicity-shingles and hematuria	Pembrolizumab	Stable disease	therapy completion	38		
12	Atezolizumab	Progressive disease	radiographic progression	Nivolumab	Stable disease	radiographic progression	10		

13	Pembrolizumab	Progressive disease	radiographic progression	Atezolizumab	Progressive disease	radiographic progression	103	Platinum-Cisplatin	Enfortumab-Vedotin
14	Atezolizumab	Stable disease	treatment related toxicity - grade 2 arthralgia	Atezolizumab	Partial response	patient preference	73		
15	Atezolizumab	Stable disease	therapy completion	Pembrolizumab	Progressive disease	radiographic progression	32	Platinum-Carboplatin	
16	Avelumab *	Progressive disease	radiographic progression	Pembrolizumab & Enfortumab-Vedotin	Complete response	-	17	Enfortumab-Vedotin (ongoing into 2nd CPI)	
17	Durvalumab & Tremelimumab	Progressive disease	radiographic progression	Pembrolizumab & Enfortumab-Vedotin	Progressive disease	radiographic progression	45	Platinum-Cisplatin	
18	Pembrolizumab	Progressive disease	clinical progression	Atezolizumab	Progressive disease	radiographic progression	22	ddMVAC	
19	Pembrolizumab	Partial response	radiographic progression	Atezolizumab	Progressive disease	radiographic progression	68		
20	Pembrolizumab	Stable disease	radiographic prog	Nivolumab	Progressive disease	radiographic progression	42	ddMVAC	

			ression						
21	Atezolizumab	Complete response	radiographic progression	Pembrolizumab	Progressive disease	radiographic progression	25		
22	Pembrolizumab*	Partial response	treatment related toxicity - grade 3 myositis	Nivolumab	Partial response	clinical progression	155	5FU/mitomycin	
23	Durvalumab	Complete response	therapy completion	Atezolizumab	Stable disease	radiographic progression	106		
24	Atezolizumab	Unknown	treatment related toxicity - grade 2 arthritis	Avelumab*	Stable disease	Patient still on treatment (26 cycles)	180	Platinum-Cisplatin	
25	Atezolizumab	Progressive disease	radiographic progression	Nivolumab	Stable disease	clinical progression	24		

*Maintenance