Treatment Rechallenge With Immune Checkpoint Inhibitors in Advanced Urothelial Carcinoma

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Abstract

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.

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 first and second 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 9 institutions who received 2 separate ICI courses. ORR with first ICI and second ICI were 39% and 13%, respectively. Most patients discontinued first ICI due to progression (n = 19) or treatment-related toxicity (n = 4). Thirteen patients received non-ICI treatment between the first and second ICI, and 12 patients changed ICI class (anti-PD-1 vs. anti-PD-L1) at rechallenge. Among 10 patients...
Checkpoint inhibitors in advanced urothelial carcinoma

who changed ICI class, 8 (80%) had progressive disease as best response with second ICI, while among 12 patients re-treated with the same ICI class, only 3 (25%) had progressive disease as best response at the time of rechallenge. With second 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 regimens 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.

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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.\(^1\) Avelumab was also FDA-approved as switch-maintenance therapy in patients with clinical benefit (response or stable disease) with frontline platinum-based chemotherapy.\(^3\) 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 (MUC) 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 regimen in a later treatment setting, either as a single agent for an approved indication or in potential combinations as part of 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 enforce-tum vedotin (EV),\(^11\) sunituzumab givitecan (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 2 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 2 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 1 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 (eg, 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 \(\chi^2\) 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 first and second ICI, respectively. We calculated ORR and disease control rate excluding the 2 patients who received second line combina-
treatment with EV and pembrolizumab. Moreover, we evaluated response to the second ICI based on response to the first ICI, response to second ICI based on the time from first ICI initiation to second ICI initiation, and response to second ICI based on whether ICI class stayed the same or changed between the 2 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 first and second 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 9 institutions in the United States and Europe who received 2 separate ICI-based regimens throughout their treatment course between 2013 and 2021. Demographic information can be found in Supplemental 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-PD-1 or anti-PD-L1 agent as monotherapy, but a subset (n = 1 for first ICI and n = 2 for second ICI) received combination treatments. One patient was treated with durvalumab and tremelimumab combination as their first 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 first ICI and second ICI-based course. However, patients receiving a second ICI had higher disease burden with more metastatic sites involved. Overall, 39% of patients demonstrated response (CR or PR) to first 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 the combination of EV and pembrolizumab at the time of rechallenge. Both patients had PD as best response to the first ICI. At the time of rechallenge 1 patient had PD and the other 1 had CR. Excluding the 2 cases that received combination EV and pembrolizumab as second line ICI (ID 16 and 17), the percentage of patients demonstrating progression as best response between first and second ICI course, was 39% and 47% accordingly. Among the 9 patients who responded to first ICI, 2 patients had PR and 2 had SD (44% disease control rate) with ICI rechallenge. Among the 4 patients who had stable disease as best response to the first ICI, 2 (50%) had disease control (1 SD and 1 PR) and 2 (50%) had PD. On the other hand, among 9 patients who had progressive disease as best response to first ICI, 4 (44%) had disease control (4 SD) at the time of rechallenge with second ICI. (Table 2).

Thirteen patients received at least one other (non-ICI) line of treatment between the first and the second 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), 2 (20%) demonstrated disease control during treatment with second ICI. On the other hand, among 12 patients re-treated with the same class of ICI, 8 (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 2 regimens; of those, 2 patients had stable disease, while 1 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 first ICI, 19 (82%) had radiographic or clinical progression, while 4 patients (17%) stopped due to treatment-related toxicity. Of those 19 who discontinued ICI due to progression, 5 patients had stable disease, 1 patient had partial response and another patient complete response as the best response to second ICI, however the latter patient received the combination EV and pembrolizumab. Of those 4 patients who stopped first ICI due to treatment-related toxicity, 2 patients had partial response and 2 patients had stable disease as best response with the second ICI. None of the patients with treatment-related toxicity to first ICI had recurrence of the same toxicity with second ICI. Regarding second 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 first ICI, while for second ICI regimen, only 1 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 first and second ICI. Two patients (ID 15 and 20) received first line ICI on a clinical trial, 2 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-tried with platinum-based chemotherapy prior to rechallenge with second 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 an
Checkpoints inhibitors in advanced urothelial carcinoma

| Table 1 | Disease Characteristics and Responses to First and Second ICIs |
|---------|---------------------------------------------------------------|
| **ECOG PS** | **First ICI** | **Second ICI** | **P-Value**<sup>a</sup> |
| 0 | 17 (68%) | 11 (44%) | 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 1.73m²)** | | | |
| 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 (x10³/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 (x10³/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%) | |

<sup>a</sup> χ² and paired t-test used for categorical and continuous variables respectively and Wilcoxon Signed Rank test for non-parametric data (PS: performance status)

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. 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 2 years among cisplatin-ineligible patients treated in the first line setting. 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. 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%. 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 (eg, NCT03606174). EV has been shown to be immunogenic in promoting recruitment and activation of immune cells. In our cohort, two patients received second ICI combined with EV, with 1 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 first ICI administration. The results of our cohort, in which none of the patients on second ICI discontinued treatment due to adverse events, are in support of prior literature suggesting that ICI rechallenge can be tolerable. 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 and survival 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 first 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 second ICI-based course as opposed to the first 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 first 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 first course, and about half of patients were rechallenged with a drug with a similar mechanism of action (anti-PD-1 after anti-PD-1, or anti-PD-L1 after anti-PD-L1). Little is currently known about any difference in response and outcomes between anti-PD-1 and anti-PD-L1 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. 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 versus 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

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**Table 2** Treatment Response and Average Time of Treatment Initiation between First and Second ICI

| Best response to first ICI | n (%) | Weeks, Median (min, max) |
|---------------------------|-------|-------------------------|
| CR+PR                     | 9 (36%) | 103.6 (17, 155) |
| Complete response         | 3 (12%) | 17.0                     |
| Partial response          | 6 (24%) | 134.0 (73, 155) |
| Stable disease            | 4 (16%) | 45.0 (10, 180)             |
| Progressive disease       | 11 (44%) | 43.5 (22, 189) |
| Unknown                   | 1 (4%)   |                         |

| Best Response to second ICI | n (%) | Weeks, Median (min, max) |
|-----------------------------|-------|-------------------------|
| CR+PR                       | 4 (16%) |                          |
| Complete response           | 1 (4%) | 103.6 (17, 155) |
| Partial response            | 3 (12%) | 17.0                     |
| Stable disease              | 8 (32%) | 134.0 (73, 155) |
| Progressive disease         | 12 (48%) | 45.0 (10, 180)             |
| Unknown*                    | 1 (4%) | 43.5 (22, 189) |

CR = Complete Response, PR = Partial Response.
*One patient missing response data.
| ID | ICI used       | Best Response         | Reason for Discontinuation | ICI Used       | Best Response         | Reason for Discontinuation | Weeks | First Interim Therapy | Second 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 response 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 | Avelumab²      | Progressive disease   | radiographic progression    | Pembrolizumab & Enfortumab-Vedotin | Complete response | -                       | 17    | Enfortumab-Vedotin (ongoing into second 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 progression    | Nivolumab      | Progressive disease   | radiographic progression   | 42    | ddMVAC                |                        |
| 21 | Atezolizumab   | Complete response     | radiographic progression    | Pembrolizumab  | Progressive disease   | radiographic progression   | 25    |                       |                        |
| 22 | Pembrolizumab² | Partial response      | treatment related toxicity-grade 3 myositis | Nivolumab      | Partial response      | clinical progression       | 155   | 5FU/mitomycin         |                        |
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 the 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 first 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.

**Clinical Practice Points**

- While immune checkpoint inhibitors (ICI) improve outcomes in a significant number of patients with advanced urothelial carcinoma (aUC), most patients do not have tumor response and almost all eventually have progressive disease
- ICI therapy remains a consideration for rechallenge in patients with aUC, given the favorable toxicity profile, especially after exhausting other therapeutic options
- In this study, we describe in detail the demographics, disease characteristics, treatment patterns and responses in patients with aUC who received two separate 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 this treatment strategy

**Authors’ Contributions**

DM, DRB, RT: Conceptualization, Methodology, Formal analysis, Investigation, Data Curation, Writing- Original Draft, Writing- Review and Editing. GI: Statistical Analysis, LND: Investigation, Data Curation, Writing- Review and Editing. TJ: Investigation, Writing- Review and Editing. NV-W: Investigation, Writing- Review and Editing. YZ: Investigation, Writing- Review and Editing. NT: Investigation, Writing- Review and Editing. NA: Investigation, Writing- Review and Editing. SD: Investigation, Writing- Review and Editing. SG: Investigation, Writing- Review and Editing. EL: Investigation, Writing- Review and Editing. AD: Investigation, Writing- Review and Editing. SL: Investigation, Writing- Review and Editing. RZ: Investigation, Writing- Review and Editing. AB: Investigation, Writing- Review and Editing. C-MF: Investigation, Writing-Review and Editing. AG: Investigation, Writing-Review and Editing. DJP: Investigation, Writing-Review and Editing. PB: Investigation, Writing-Review and Editing. PG: Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing- Original Draft, Writing- Review and Editing, Supervision. ARK: Conceptualization, Methodology, Software, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing-Original Draft, Writing- Review and Editing, Supervision. VSK: Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing- Original Draft, Writing- Review and Editing, Supervision.

**Disclosure**

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Checkpoint inhibitors in advanced urothelial carcinoma

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Supplementary materials

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