

Durable responses in patients with genitourinary cancers following immune checkpoint therapy rechallenge after moderate-to-severe immune-related adverse events

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ABSTRACT

Background Immune checkpoint therapy (ICT) prolongs survival in subsets of patients with cancer but can also trigger immune-related adverse events (irAEs) requiring treatment discontinuation. Recent studies have investigated safety of ICT rechallenge after irAEs, and evidence suggests that rechallenge may be associated with improved antitumor responses. However, data are limited on response duration after ICT rechallenge, particularly after severe irAEs.

Objective To evaluate safety and efficacy of ICT rechallenge after moderate-to-severe irAEs in patients with renal cell carcinoma (RCC), urothelial carcinoma (UC), and prostate cancer.

Methods In this retrospective cohort study, medical records from September 25, 2013, to June 1, 2020, for patients with genitourinary (GU) cancers at MD Anderson Cancer Center who were rechallenged with the same or different ICT following irAEs were reviewed. Demographics, ICT exposure, irAEs (grade and treatment), ICT discontinuation or rechallenge, rates of subsequent irAEs (new or recurrent) and antitumor activity (objective response rates and response duration) were reviewed.

Results Sixty-one patients with RCC, UC, and prostate cancer were rechallenged with ICT after experiencing 105 total irAEs. Objective response rates after rechallenge, that is, upgrade in response, were 14% in RCC (4/28), 21% in UC (3/14), and 0% in prostate cancer. All seven patients who achieved upgrade in response had initial grade 2 or 3 irAEs. Responses were durable among these seven patients, with median radiographic progression-free survival not reached (range: 3.7–66.4 months) as of the March 8, 2021, data cut-off (median follow-up 40.9 months (95% CI 35.3 to 46.5)). All achieved complete response except one patient who was lost to follow-up. The rate of subsequent grade 3 or 4 irAEs after rechallenge was 30%, with no fatal irAEs. The rate of recrudescence of the same irAE was 26% (16/61), 54% of patients received corticosteroids (33/61), and 21%

received targeted immunosuppression (13/61) for the initial irAEs.

Conclusions and relevance ICT rechallenge after moderate-to-severe irAEs was associated with deep and durable responses in a subset of patients with RCC and UC, with acceptable safety and no fatal events. Strategies to enable ICT resumption after moderate-to-severe irAEs, such targeted immunosuppression, warrant further study.

INTRODUCTION

Immune checkpoint therapies (ICTs), most commonly targeting cytotoxic T lymphocyte-associated protein-4 (CTLA-4), programmed cell death protein-1 (PD-1), and/or programmed death-ligand 1 (PD-L1) have dramatically altered the treatment paradigm for many cancers, offering prolonged survival for subsets of patients. ICTs are standard-of-care therapy for patients with renal cell carcinoma (RCC) and urothelial carcinoma (UC).^{1,2}

ICTs carry the risk of immune-related adverse events (irAEs), in which excess immune activation can lead to damage of normal host tissue. Though irAEs most commonly affect the skin, gastrointestinal tract and endocrine systems, irAEs can affect any organ including cardiovascular, pulmonary, musculoskeletal and nervous systems, among others. irAEs vary in severity, ranging from mild events in which ICT can often be continued to severe irAEs warranting cessation of therapy and aggressive immunosuppression. In general, management guidelines recommend continuation of ICT for most grade 1 irAEs (defined by the Common Terminology Criteria for Adverse Events

(CTCAE)), whereas grade 2 irAEs usually warrant ICT interruption, treatment with corticosteroids, and consideration of ICT resumption when the irAE returns to grade 1 or has resolved.³ Grade 3 irAEs typically require high-dose corticosteroids in addition to withholding ICT and often involve additional, targeted immunosuppression.

Multiple studies have demonstrated a link between manageable, non-fatal irAEs and improved outcomes in patients with cancer.^{4–18} The mechanisms of these augmented antitumor outcomes are incompletely defined, but may be due in part to shared antigens between host and tumor, which may enable effective antitumor T cell responses within the context of excess immune activation during irAEs.¹⁹ Importantly, such studies have often reported that immunosuppressive treatment of irAEs does not necessarily reduce the antitumor efficacy of ICTs. However, prolonged exposure to high-dose corticosteroids is associated with serious adverse effects, including life-threatening opportunistic infection, hyperglycemia, and myopathy, among others, highlighting the need for steroid-sparing immunosuppression to abort the toxicity. In certain cases, rechallenge with ICTs has been associated with antitumor responses in patients not previously responding to ICT.^{20,21} Taken together, these studies suggest that the risk–benefit calculation may favor rechallenge with ICTs after irAEs in selected circumstances, possibly aided by selective immunosuppression.²² Studies of ICT rechallenge after irAEs to date have primarily focused on one type of cancer such as melanoma, RCC, or lung cancer, or have provided limited clinical details on treatment, severity, or cancer-specific outcomes, including duration of response.^{20,21,23}

Given that ICTs can induce prolonged responses in subsets of patients with cancer, we hypothesized that ICT rechallenge after irAEs would be not only safe in selected circumstances but may lead to augmented, durable responses. In this retrospective study, we report on a cohort of patients with RCC, UC, and prostate cancer, who underwent ICT rechallenge after moderate-to-severe irAEs and achieved improved, durable responses in a subset of patients with RCC and UC, with an acceptable safety profile and no fatal events.

METHODS

Medical records of patients with RCC, UC, and prostate cancer treated at MD Anderson Cancer Center (MDACC) from September 25, 2013, to June 1, 2020, were queried using a set of 202 pre-specified search terms covering ICT (including generic names, trade names, and chemical names) and a broad set of autoimmune diseases encompassing irAEs, including abbreviations (online supplemental table 1). Patients' records were manually reviewed to confirm administration of ICT and documentation of irAEs, permanent discontinuation or rechallenge with ICT, grade of irAE by CTCAE, and treatment. Data on demographics and outcomes were also collected. The data cut-off date for survival was March 8, 2021. Patient

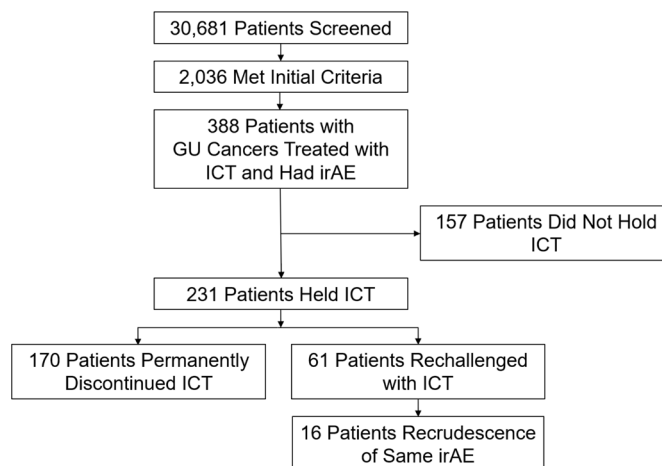


Figure 1 Consort diagram. Medical records from patients with prostate cancer, urothelial carcinoma, and renal cell carcinoma were screened for exposure to ICT and experience of irAE using pre-specified search terms. ICT, immune checkpoint therapy; irAE, immune-related adverse event; GU, genitourinary.

and disease characteristics were summarized as median and range for continuous variables, and as number and percentage for categorical variables. Radiographic responses were screened by RECIST V.1.1 where available (ie, when measurements were formally listed as part of a clinical protocol); otherwise, the response assessment of the treating physician was used. Response upgrades were subsequently confirmed by two independent radiologists by RECIST V.1.1. The decision to rechallenge with ICT was at the discretion of the treating physician. All statistics were descriptive in nature and no formal statistical hypotheses were tested. Kaplan-Meier survival curves were generated in GraphPad Prism V.8.0.0. Median follow-up time was calculated by the reverse Kaplan-Meier method.

RESULTS

In the initial screen, 30,681 patient records were queried using pre-specified search terms (online supplemental table 1), filtered to 231 patients with RCC, UC, or prostate cancer who experienced irAEs after ICT requiring suspension of treatment (figure 1). Sixty-one patients were identified who were rechallenged with the same or different ICT (RCC, n=28; UC, n=14; prostate cancer, n=19) (figure 1) (table 1). Eight of the 19 patients with prostate cancer (42%) had RECIST-measurable disease (table 1). Thirty-eight out of the 61 patients (62%) were rechallenged with their original ICT (ICT1) (online supplemental table 2). A subset of patients were rechallenged with a separate, second ('ICT2') or third ('ICT3') ICT agent, with overlaps between these groups, that is, patients who were rechallenged with both ICT1 and ICT2 (table 2). The relationship between the initial ICT drug class to the next line ICT exposure is provided in online supplemental table 3. Details of the reasons for ICT1 discontinuation are provided in online supplemental

Table 1 Baseline characteristics of patients rechallenged with immune checkpoint therapy (ICT)

ICT rechallenge patients (n=61)	
Age, median (minimum, maximum)	65 (38–90)
Sex, n (%)	
Male	50 (82)
Female	11 (18)
Cancer, n (%)	
RCC	28 (46)
Clear cell (only)	20 (71)
Clear cell with rhabdoid and/or sarcomatoid features	7 (25)
Papillary (type 1)	1 (4)
Urothelial carcinoma	14 (23)
Bladder cancer	12 (86)
Upper tract urothelial carcinoma	2 (14)
Prostate adenocarcinoma	19 (31)
IMDC risk score for RCC	
Favorable risk	6 (21)
Intermediate/poor risk	22 (79)
Metastatic disease at diagnosis, n/N (%)	36/61 (59)
RCC	16/28 (57)
Urothelial carcinoma	7/14 (50)
Bone metastases	2/14 (14)
Liver metastases	1/14 (7)
Prostate adenocarcinoma	13/19 (68)
RECIST-measurable disease	8/19 (42)
Front-line ICT, n (%)	20 (33)
Median number of prior therapies (IQR)	
RCC	1 (0–1)
Urothelial carcinoma	1 (0–1)
Prostate adenocarcinoma	1 (0–2)
Prior therapies received, n (%)	
RCC	
Sunitinib	6 (21)
Pazopanib	5 (18)
Cabozantinib	3 (11)
Axitinib	2 (7)
Everolimus	2 (7)
Urothelial carcinoma	
MVAC	6 (43)
Gemcitabine/cisplatin	4 (29)
Prostate adenocarcinoma	
Docetaxel	7 (37)
Cabazitaxel	1 (5)
Sipuleucel-T	7 (37)
Radium-223	2 (11)
Abiraterone	14 (74)

Continued

Table 1 Continued

ICT rechallenge patients (n=61)

Enzalutamide	8 (42)
Any NHT	18 (95)

IMDC, International Metastatic RCC Database; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; NHT, next-generation hormonal therapy; RCC, renal cell carcinoma.

table 4. The median time from first dose of ICT1 to discontinuation (last dose of ICT1) was 84 days (95% CI: 65 to 105).

The 61 patients rechallenged with ICT had experienced a total of 105 initial irAEs (table 3). The median time to the development of irAEs from ICT1 was 56 days (95% CI: 42 to 65). The majority of initial irAEs were moderate (grade 2) and included a subset of severe irAEs (grade 3 or 4). The most common irAEs of any grade were rash/pruritus, colitis/diarrhea, and thyroid abnormalities. The grade 3 irAEs consisted of rash/pruritus, colitis/diarrhea, hepatitis/elevated aspartate aminotransferase/alanine aminotransferase (AST/ALT), arthritis/arthralgia, pancreatitis, elevated amylase/lipase, and dyspnea/pleural effusion (table 3). There was one grade 4 irAE: hepatitis/elevated AST/ALT (table 3). There were no cases of the more often lethal cardiac or neuromuscular irAEs (myocarditis, myositis, or myasthenia gravis) in the cohort of patients rechallenged with ICT. Corticosteroids were administered in 54% of patients (33/61), and 21% of patients received targeted immunosuppression (13/61) for the initial irAEs (online supplemental table 5). Targeted immunosuppression included mesalazine, vedolizumab, infliximab, tocilizumab, and mycophenolate mofetil.

Thirty-six out of the 61 patients rechallenged with ICT (59%) experienced a total of 46 subsequent irAEs (table 3). The median time to first subsequent irAE after rechallenge was 116 days (95% CI: 56 to 268). Sixteen patients (26%) had recrudescence of the same irAE. Similar recrudescence rates were observed with rechallenge after grade 2 irAEs (26%, 9/34) and after grade 3/4 irAEs (20%, 3/15) ($p=0.73$, Fisher's exact test). The rate of irAEs after rechallenge in patients who received corticosteroids for the initial irAE was 58% (19/33) and 61% (17/28) in those patients who did not receive corticosteroids. Most subsequent irAEs were grade 1 or grade 2 (table 3). The most common subsequent irAEs were rash/pruritus, colitis/diarrhea, and hepatitis/elevated AST/ALT (table 3). The breakdown of subsequent irAEs by rechallenge agent is provided in online supplemental table 7, and had an expected distribution (ie, colitis/diarrhea occurred most frequently following rechallenge with anti-CTLA-4-based regimens). There were 14 subsequent grade 3 irAEs (30%), including colitis/diarrhea, hepatitis/elevated AST/ALT, arthritis/arthralgia, pneumonitis, adrenal insufficiency, and type 1 diabetes mellitus

Table 2 ICT received in rechallenged patients

All patients (n=61)	ICT1 (%) n=61	ICT2 (%) n=34	ICT3 (%) n=7
<i>Anti-PD-(L)1 monotherapy</i>	7 (11)	23 (68)	2 (29)
<i>Anti-CTLA-4 monotherapy</i>	10 (16)	0 (0)	0 (0)
<i>Anti-CTLA-4+anti-PD-(L)1</i>	23 (38)	2 (6)	1 (14)
<i>Anti-PD-(L)1+TKI</i>	6 (10)	6 (18)	3 (43)
<i>Anti-CTLA-4+anti-PD-(L)1+TKI</i>	1 (2)	0 (0)	0 (0)
<i>Anti-PD(L)1+other</i>	14 (23)	3 (9)	1 (14)
Renal cell carcinoma (n=28)	ICT1 (%) n=28	ICT2 (%) n=18	ICT3 (%) n=5
<i>Anti-PD-(L)1 monotherapy</i>	3 (11)	11 (61)	1 (20)
<i>Anti-CTLA-4 monotherapy</i>	1 (4)	0 (0)	0 (0)
<i>Anti-CTLA-4+anti-PD-(L)1</i>	10 (36)	0 (0)	1 (20)
<i>Anti-PD-(L)1+TKI</i>	6 (21)	6 (33)	3 (60)
<i>Anti-CTLA-4+anti-PD-(L)1+TKI</i>	1 (4)	0 (0)	0 (0)
<i>Anti-PD(L)1+other</i>	7 (25)	1 (6)	0 (0)
Urothelial carcinoma (n=14)	ICT1 (%) n=14	ICT2 (%) n=7	ICT3 (%) n=2
<i>Anti-PD-(L)1 monotherapy</i>	4 (29)	4 (57)	1 (50)
<i>Anti-CTLA-4 monotherapy</i>	3 (21)	0 (0)	0 (0)
<i>Anti-CTLA-4+anti-PD-(L)1</i>	3 (21)	1 (14)	0 (0)
<i>Anti-PD(L)1+other</i>	4 (21)	2 (28)	1 (50)
Prostate cancer (n=19)	ICT1 (%) n=19	ICT2 (%) n=9	ICT3 (%) n=0
<i>Anti-PD-(L)1 monotherapy</i>	0 (0)	8 (89)	0 (0)
<i>Anti-CTLA-4 monotherapy</i>	6 (32)	0 (0)	0 (0)
<i>Anti-CTLA-4+anti-PD-(L)1</i>	10 (53)	0 (0)	0 (0)
<i>Anti-PD(L)1+other</i>	3 (16)	1 (11)	0 (0)

*'ICT1' refers to the first checkpoint therapy to which the patient was exposed, 'ICT2' the second, and 'ICT3' the third.

CTLA-4, cytotoxic T lymphocyte-associated protein-4; ICT, immune checkpoint therapy; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; TKI, tyrosine kinase inhibitor.

(table 3). Eight of these 14 (57%) received systemic corticosteroids, with a median duration of steroids of 39 days (range: 15–69). There were no grade 4 or 5 irAEs. The relationship between type and grade of initial and subsequent irAEs is shown in figure 2. The most common initial irAEs leading to a subsequent irAE after rechallenge were colitis and rash (figure 2). One episode of grade 3 colitis was noted after an initial episode of grade 1 colitis, and cases of grade 3 hepatitis and colitis were identified after a grade 1 rash (figure 2). No cases of subsequent cardiac or neuromuscular irAEs (myocarditis, myositis, or myasthenia gravis) were observed in patients rechallenged with ICT.

We next examined efficacy outcomes with ICT rechallenge (figure 3). As of the March 8, 2021, data cut-off, the median follow-up time was 40.9 months (95% CI 35.3 to 46.5). The median time from first irAE to assessment of best radiographic response following rechallenge was 4.3 months (95% CI: 3.2 to 6.5). Survival outcomes are summarized in figure 3 and online supplemental table 8. Response upgrades were confirmed by two independent

radiologists by RECIST V.1.1, and measurements for patients with upgrade in response are provided in online supplemental table 9. For the patients with RCC, three patients achieved a subsequent complete response (CR) from partial response (PR) after ICT rechallenge, and one patient reached a subsequent PR from stable disease (SD) (14%, 4/28) (figure 3C) (online supplemental table 4 and online supplemental table 9). In the patients with UC (n=14), three patients achieved CR from SD, including one patient (#60) who had undergone a consolidative surgery to resect residual tumor (21%, 3/14) (figure 3C) (online supplemental table 4 and online supplemental table 9). Among the patients with prostate cancer (eight patients with RECIST-measurable disease) no patients achieved an upgrade in response following ICT rechallenge (figure 3C) (online supplemental table 8). Details of the seven patients with UC and RCC who achieved an upgrade in response, all of whom had initial grade 2 or 3 irAEs, are summarized in table 4 and online supplemental table 10. One of these seven patients discontinued treatment for toxicity, one remains on treatment, and the

Table 3 Initial and subsequent irAEs in patients rechallenged with ICT

Initial irAEs	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)	Total N (%)
All	31 (30)	57 (54)	16 (15)	1 (1)	105 (100)
Rash/pruritus	15 (14)	12 (11)	4 (4)	0 (0)	31 (30)
Colitis/diarrhea	5 (5)	9 (9)	7 (7)	0 (0)	21 (20)
Hypothyroidism/hyperthyroidism/thyroiditis	1 (1)	14 (13)	0 (0)	0 (0)	15 (14)
Hepatitis/elevated AST/ALT	5 (5)	2 (2)	1 (1)	1 (1)	9 (9)
Arthritis/arthralgia	3 (3)	4 (4)	1 (1)	0 (0)	8 (8)
Hypophysitis	0 (0)	4 (4)	0 (0)	0 (0)	4 (4)
Pancreatitis	0 (0)	3 (3)	1 (1)	0 (0)	4 (4)
Pneumonitis	2 (2)	2 (2)	0 (0)	0 (0)	4 (4)
Elevated amylase/lipase	0 (0)	1 (1)	1 (1)	0 (0)	2 (2)
Adrenal insufficiency	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Dyspnea/pleural effusion	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
Eosinophilia	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Hypersensitivity reaction	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Polymyalgia rheumatica	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Psoriasis	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Uveitis	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Subsequent irAEs	Grade 1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)	Total N (%)
All	11 (24)	21 (46)	14 (30)	0 (0)	46 (100)
Rash/pruritus	5 (11)	5 (11)	0 (0)	0 (0)	10 (22)
Colitis/diarrhea	1 (2)	2 (4)	5 (11)	0 (0)	8 (17)
Hepatitis/elevated AST/ALT	1 (2)	2 (4)	5 (11)	0 (0)	8 (17)
Arthritis/arthralgia	3 (7)	2 (4)	1 (2)	0 (0)	6 (13)
Hypothyroidism	0 (0)	4 (9)	0 (0)	0 (0)	4 (9)
Pneumonitis	0 (0)	2 (4)	1 (2)	0 (0)	3 (7)
Adrenal insufficiency	0 (0)	1 (2)	1 (2)	0 (0)	2 (4)
Type 1 diabetes mellitus	0 (0)	1 (2)	1 (2)	0 (0)	2 (4)
Pancreatitis	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)
Peripheral neuropathy	1 (2)	0 (0)	0 (0)	0 (0)	1 (2)
Nephritis	0 (0)	1 (2)	0 (0)	0 (0)	1 (2)

All events graded by Common Terminology Criteria for Adverse Events (CTCAE) V.5.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

remainder either completed treatment as pre-specified in a clinical protocol or were lost to follow-up (table 4). The median progression-free survival (PFS) has not yet been reached for these seven patients (range: 3.7–66.4 months) (figure 3D). The patient with the shortest PFS (3.7 months, #13) was lost to follow-up and had achieved a PR at the time of last response assessment (figure 3D). Among these seven patients, three patients had recrudescence of the same irAE after rechallenge. Subsequent irAEs among these patients were predominantly grade 1 and 2, with the exception of grade 3 hepatitis in one patient who achieved a subsequent CR after PR (table 4). Finally, clinical information on the four patients who demonstrated a ‘downgrade’ in response, is provided in online supplemental table 11.

We then examined the influence of targeted immunosuppression (including biologics) on outcomes and identified 13 cases in which selective treatment enabled ICT rechallenge (RCC, n=7; UC, n=3; prostate cancer, n=3) (table 5). Nine of these 13 (69%) had been treated with corticosteroids (table 5). These 13 cases included colitis/diarrhea, arthritis, psoriasis, and hepatitis. For colitis, patients received mesalamine, infliximab (anti-tumor necrosis factor- α) and/or vedolizumab (anti-integrin $\alpha 4\beta 7$) (table 5). Two patients with arthritis received tocilizumab (anti-interleukin (IL)-6), and one patient with psoriasis received secukinumab (anti-IL-17A) (table 5). There were seven subsequent irAEs, predominantly grade 1 or 2 with the exception of one grade 3 colitis. Notably, two patients with RCC achieved a subsequent response

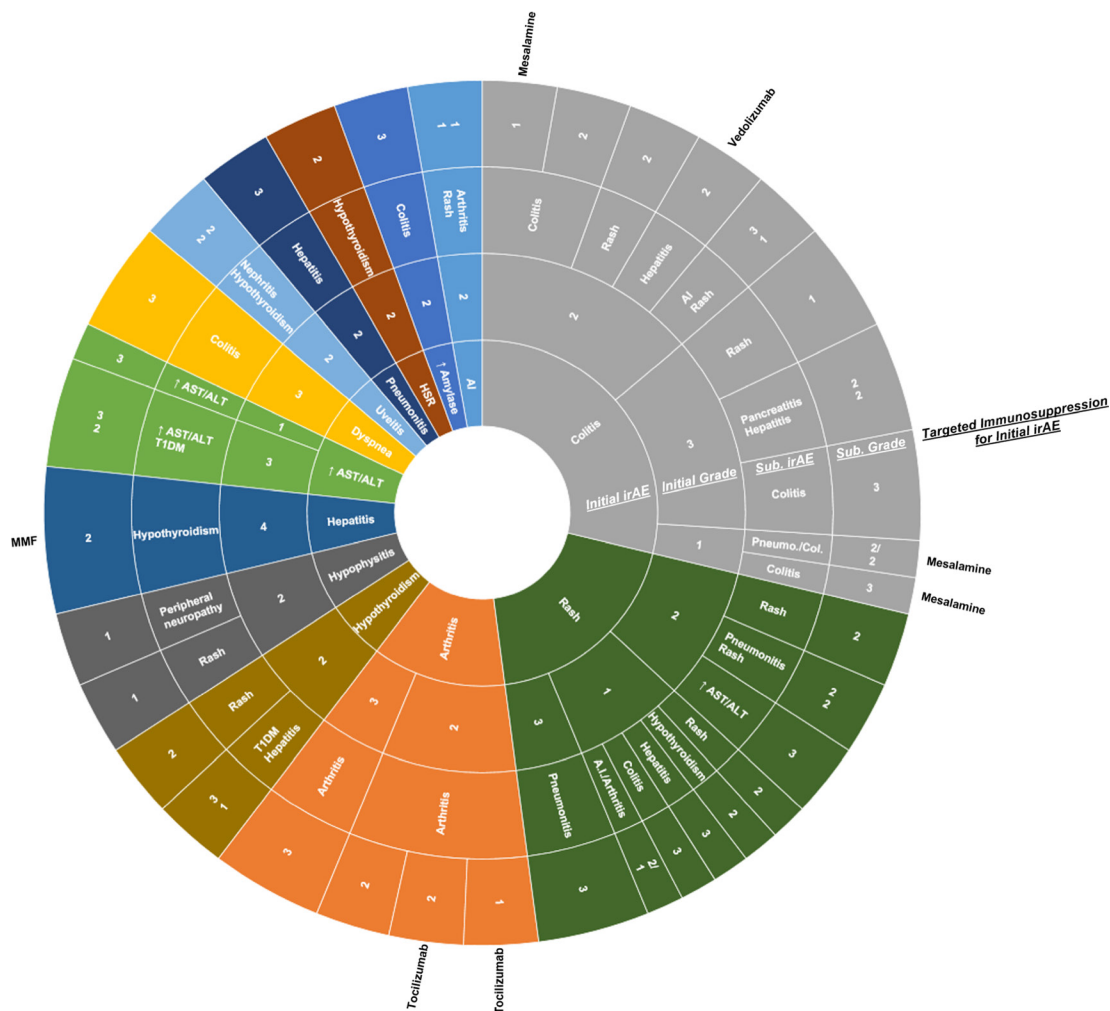


Figure 2 Patterns of initial and subsequent irAEs. ‘Arthritis’ includes both arthritis and arthralgia. ‘Colitis’ includes both biopsy proven colitis and suspected. For patients with multiple initial irAEs, the highest grade or most clinically relevant (eg, warranting hospitalization) event is depicted for readability. Pie slices generated for legibility and do not correlate with frequency of irAE. Patients who did not experience a subsequent irAE (n=25) are not included in this diagram. AI, adrenal insufficiency; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Col., colitis; HSR, hypersensitivity reaction; irAEs, immune-related adverse events; MMF=mycophenolate mofetil; Pneumo., pneumonitis; Subs. subsequent; T1DM, type 1 diabetes mellitus.

upgrade with selective immunosuppression (SD to PR, n=1; PR to CR, n=1), who had colitis/diarrhea, of whom one received vedolizumab and one received mesalamine (table 5). Of these 13 patients, 7 experienced a subsequent irAE (54%), which were predominantly grade 1 or 2, with the exception of one subsequent case of grade 3 colitis/diarrhea, which occurred following rechallenge with anti-CTLA-4 monotherapy after grade 1 colitis/diarrhea (table 5). Corticosteroids were required in two of these seven cases (29%). Vedolizumab was employed in one case of grade 3 colitis, and tocilizumab was employed in two cases of grade 1 and grade 2 arthritis/arthralgia, respectively (table 5).

Finally, because it has recently been observed that irAE involvement in target organs (eg, interstitial nephritis in patients with RCC) may be associated with increased response to ICT, potentially due to antigenic overlap between renal tubular cells and tumor cells, we identified one patient with RCC, who had grade 2 nephritis as a

subsequent irAE after initial grade 2 uveitis.²⁴ This patient achieved a durable partial response lasting 30 months from the start of ICT, with a time to subsequent treatment of 25.9 months.

DISCUSSION

In this retrospective cohort study, we investigated ICT rechallenge following moderate-to-severe irAEs in patients with RCC, UC, and prostate cancer. We hypothesized that ICT rechallenge after irAEs would be safe in selected circumstances and could lead to augmented, durable responses. We observed that ICT rechallenge after moderate-to-severe irAEs was associated with deep and durable responses in a subset of patients with RCC and UC, with an acceptable safety profile and no fatal events.

For patients with treatment-refractory cancers and limited therapeutic options, the ability to rechallenge

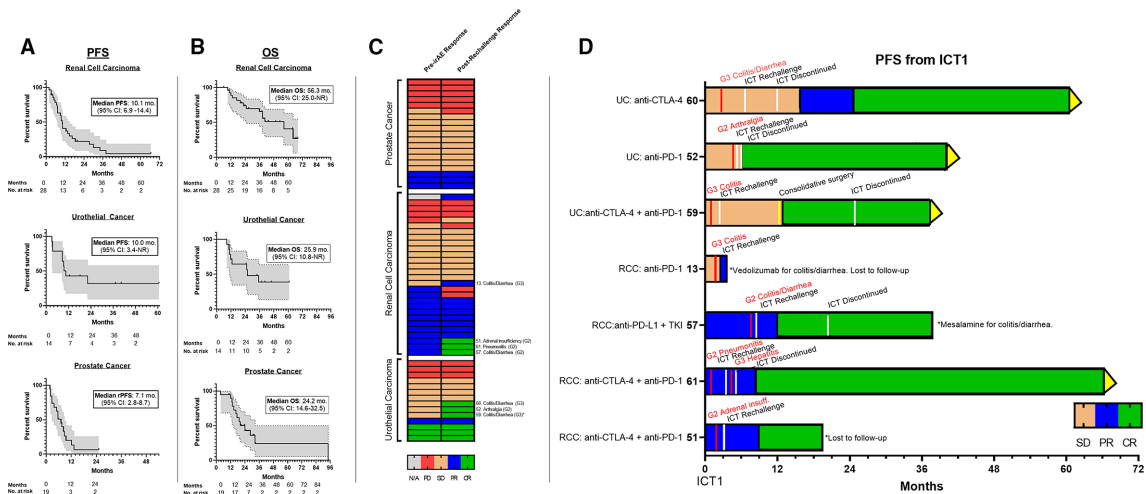


Figure 3 Outcomes with ICT rechallenge. (A) Progression-free survival (PFS) after first exposure to ICT (ICT1). Initial screening radiographic response assessment obtained per RECIST V.1.1 where available. Radiographic PFS (rPFS) used for patients with prostate cancer. (B) Overall survival (OS) after ICT1. (C) Best radiographic response after irAE. irAEs are annotated for seven patients (four RCC and three UC) with response upgrade. Response upgrades confirmed by two independent radiologists. (D) Swimmer's plot of PFS after ICT1 (months) in patients with response upgrades. Response upgrades confirmed by two independent radiologists. Yellow arrows indicate ongoing response. CR, complete response; CTLA-4, cytotoxic T lymphocyte-associated protein-4; ICT, immune checkpoint therapy; irAE, immune-related adverse event, PD, progression of disease; PD-1 programmed cell death protein-1; PD-L1, programmed death-ligand 1; PR, partial response; RCC, renal cell carcinoma; SD, stable disease; TKI, tyrosine kinase inhibitor; UC, urothelial carcinoma. *Indicates patient who underwent consolidative surgery.

with ICT offers a potential strategy for clinical benefit. Prior studies have reported an acceptable rate of irAE recrudescence following ICT rechallenge in selected circumstances with additional antitumor responses in certain cases (online supplemental table 10).^{20 21 25} From the standpoint of safety, the rate of recrudescence of the same irAE in our cohort was 26.2% (16/61), in line with other reports of ICT rechallenge.^{20 25–27} The rate of subsequent grade 3 or 4 adverse events was 30% after rechallenge, with no fatal complications observed. Importantly, our data show that select patients with severe (grade 3) irAEs were able to be successfully rechallenged with ICT, enabled in certain cases by targeted immunosuppression. The patterns of initial and subsequent irAEs were as expected, with dermatologic, gastrointestinal, joint, and endocrine irAEs as the most common. Of note, our cohort does not provide data on rechallenge after toxicities associated with high fatality rates such as myocarditis and myasthenia gravis (these cases were present only in those patients who permanently discontinued ICT). The largest pharmacovigilance study of ICT rechallenge to date examined 452 informative rechallenges and identified a rate of recrudescence of 28.8%.²⁵ This study shed light on patterns of recurrence (eg, finding that the highest recurrence rates were in colitis and hepatitis); however, it did not report data on severity or treatment of irAEs nor on cancer-specific outcomes. Additionally, only rechallenge with the same ICT regimen was reported. Other studies have identified recrudescence rates across tumor types and ICT classes ranging from 3% to 43% (online supplemental table 12).^{20 26–30} Finally, we observed a longer median time to subsequent irAEs after rechallenge, compared with the time for the development

of initial irAEs. Possible explanations for this longer latency period for the development of a subsequent irAE include: (1) effects of corticosteroids or other immunosuppression and (2) diminished immune activation due to rechallenge with only one drug (eg, rechallenge with anti-PD(L)1 only following combined anti-CTLA-4 and anti-PD(L)1). This observation will require further validation in future studies.

Beyond the issue of safety, a key question is whether ICT rechallenge after irAEs is associated with improved outcomes. In a retrospective study of 173 patients with metastatic melanoma who developed gastrointestinal (GI) irAEs, any grade GI irAEs were associated with improved OS compared with patients who did not experience GI irAEs, with no impact on survival with the use of immunosuppressive treatment.³¹ This association between irAEs and antitumor response without harmful impact from immunosuppression has been borne out in numerous studies across multiple cancer types, including urothelial carcinoma, melanoma, renal cell carcinoma, and lung cancers.^{4–18 32} Moreover, evidence suggests that ICT rechallenge may lead to an antitumor effect for patients with irAEs who had not previously experienced a treatment response, as has been shown in non-small cell lung cancer and melanoma.^{27 28} Two separate studies of ICT rechallenge in RCC have reported objective response rates of 23%.^{20 21} These studies included subsets of patients with grade 3 toxicities, but did not provide information on immunosuppression beyond corticosteroids. In our patients, we observed objective response rates of 14% in RCC, 21% in UC, and 0% in prostate cancer (in eight patients with RECIST-measurable disease) following ICT rechallenge. It is important to note that ICT is not

Table 4 Clinical information for patients who achieved subsequent upgrade in response after ICT rechallenge

Pt.	Age	Sex	Cancer	Alive	OS from ICT1 (Mo.)	OS from ICT1 and post-ICT1	PFS from ICT1 (Mo.)	Initial irAE	Initial irAE grade	Initial irAE	Other immunosupp.	Steroid	Other	Other initial irAE	ICT rechallenge drug	Reason ICT1 stopped	Imaging response pre-rechall. and post-rechall.	Same irAE after rechall.	Subseq. irAE
13	65	M	RCC	LTFU	6	PR*	3.7	Colitis/diarrhea	3	Y	Vedo.	Y	N/A	None	Anti-PD-(L)1	LTFU	PR*	N	NA
51	42	M	RCC	LTFU	21	PR	19.6	AI (HC)	2	Y (HC)	N/A	Y (HC)	N/A	Thyroiditis (G2) rash/pruritus	Anti-CTLA-4+Anti-PD-(L)1	Therapy complete	CR	Y	Arthralgia (G1)
52	87	M	UC	Y	40.5	SD	40.3	Arthralgia	2	Y	N/A	Y	N/A	None	Anti-PD-(L)1	Therapy complete	CR	Y	Arthralgia (G2)
57	56	M	RCC	Y	40.9	PR	37.9	Colitis/diarrhea	2	Y	Mes.	Y	Mes.	Rash/pruritus (G1)	Anti-PD-(L)1+TKI	Therapy ongoing	CR	Y	Diarrhea (G1)
59	41	M	UC	Y	46	SD	37.3	Colitis/diarrhea	3	Y	N/A	Y	N/A	None	Anti-CTLA-4+Anti-PD-(L)1	Therapy complete	CR**	N	Rash (G1)
60	72	M	UC	Y	60.8	SD	60.6	Colitis/diarrhea	3	Y	N/A	Y	N/A	Rash/pruritus (G1)	Anti-CTLA-4	Therapy complete	CR	N	NA
61	54	F	RCC	Y	66.5	PR	66.4	Pneumonitis	2	Y	N/A	Y	N/A	Thyroiditis (G2)	Anti-CTLA-4+Anti-PD-(L)1	Toxicity	CR	N	Hepatitis (G3)

*First restaging imaging occurred after irAE.

AI, adrenal insufficiency; CR, complete response; CTLA-4, cytotoxic T lymphocyte-associated protein-4; HC, hydrocortisone; ICT, immune checkpoint therapy; Immunosupp., immunosuppression; irAE, immune-related adverse event; LTFU, lost to follow-up; Mes, mesalazine; Mo., month; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; Pt., patient; RCC, renal cell carcinoma; rechall., rechallenge; SD, stable disease; subseq., subsequent; TKI, tyrosine kinase inhibitor; UC, urothelial carcinoma; Vedo, vedolizumab.

Table 5 Clinical details of ICT rechallenged patients who received targeted immunosuppression for initial irAE

Pt. Age	Sex	OS from ICT1 (Mo.)	PFS from ICT1 (Mo.)	Primary cancer	ICT1	Initial irAE	Initial irAE grade	Initial irAE steroid	Other immune suppression for initial irAE	ICT rechallenge drug	Imaging response after rechallenge	Same irAE after rechallenge	Subs. irAE	Subs. irAE grade	Other immune suppression for subs. irAE	
16	53	M	19.6	4.8	RCC	Anti-CTLA-4+Anti-PD-(L)1	Hepatitis	4	Yes	Mycophenolate mofetil	Anti-PD-(L)1+TKI	PR	No	Hypothyroid	2	None
47	50	M	30.7	10.4	RCC	Anti-CTLA-4+Anti-PD-(L)1+TKI	Colitis/diarrhea	3	Yes	Vedolizumab+FMT	Anti-PD-(L)1 monotherapy	PD	No	None	None	None
9	49	M	10.9	3	RCC	Anti-CTLA-4 monotherapy	Colitis/diarrhea	3	Yes	Infliximab	Anti-PD-(L)1+TKI	PD	No	None	None	None
43	50	M	28.9	12.5	RCC	Anti-PD(L)1+other	Colitis/diarrhea	2	Yes	Vedolizumab	Anti-PD-(L)1+TKI	PR	No	Hepatitis	2	None
57	56	M	34.6	33.4	RCC	Anti-PD-(L)1+TKI	Colitis/diarrhea	2	Yes	Mesalamine	Anti-PD-(L)1+TKI	CR	Yes	Colitis/diarrhea	1	None
13	65	M	6	3.7	RCC	Anti-PD-(L)1 monotherapy	Colitis/diarrhea	3	Yes	Vedolizumab	Anti-PD-(L)1 monotherapy	PR	No	None	None	None
38	59	M	16.8	10.3	RCC	Anti-PD-(L)1+TKI	Colitis/diarrhea	1*	Yes	Infliximab	Anti-PD-(L)1+TKI	SD	No	None	None	None
49	68	F	27.3	10.5	UC	Anti-CTLA-4+Anti-PD-(L)1	Psoriasis	2	No	Secukinumab	Anti-PD-(L)1	CR	No	None	None	None
42	64	M	26.6	12.5	UC	Anti-PD(L)1+other	Arthritis	2	Yes	Tocilizumab	Anti-PD-(L)1+other	PR	Yes	Arthralgia	1	Tocilizumab
34	70	F	25.3	22.2	UC	Anti-PD(L)1+other	Arthritis	2	Yes	Tocilizumab	Anti-PD-(L)1+other	SD	Yes	Arthritis	2	Tocilizumab
3	47	M	20.2	2.1	Prostate cancer	Anti-CTLA-4+Anti-PD-(L)1	Colitis/diarrhea	2	No	Mesalamine	Anti-PD-(L)1 monotherapy	PD	No	None	None	None
22	76	M	16.5	7.1	Prostate cancer	Anti-CTLA-4 monotherapy	Colitis/diarrhea	1	No	Mesalamine	Anti-CTLA-4 monotherapy	SD	Yes	Colitis/diarrhea	3	Vedolizumab
2	55	M	13.1	1.8	Prostate cancer	Anti-CTLA-4+Anti-PD-(L)1	Colitis/diarrhea	1	No	Mesalamine	Anti-CTLA-4+anti-PD-(L)1	PD	Yes	Pneumonitis colitis/diarrhea	2	None

*Patient treated with infliximab for persistent symptoms despite steroids.

CR, complete response; CTLA-4, cytotoxic T lymphocyte-associated protein-4; FMT, fecal microbiota transplantation; ICT, immune checkpoint therapy; irAE, immune-related adverse event; Mo., month; OS, overall survival; PD, progressive disease; PD-L1, programmed death-ligand 1; PFS, progression free survival (radiographic PFS for prostate cancer); PR, partial response; Pt., patient; RCC, renal cell carcinoma; SD, stable disease; Subs., subsequent; TKI, tyrosine kinase inhibitor; UC, urothelial carcinoma.



approved by the Food and Drug Administration for prostate cancer except in certain tumor-agnostic settings, and significant effort is underway in optimizing patient selection (including sites of disease, eg, bone-predominant vs lymph node vs visceral metastases).³³ All seven patients who achieved a subsequent upgrade in response had experienced grade 2 or 3 irAEs. Two patients with RCC achieved a response upgrade following selective immunosuppression after grade 2 or 3 colitis. Most notably, these responses were durable and deep, with median PFS not yet reached as of the March 8, 2021, data cut-off date, and six of the seven patients achieving CR. The patient with the shortest PFS had a partial response at the time of last response assessment and was lost to follow-up. Notably, while the classes of second-line ICTs in our cohort were diverse, among those patients with upgrade in response, all of the patients were rechallenged with a similar class of drug or only one of the two drugs (eg, anti-PD-(L)1 following anti-CTLA-4 plus anti-PD-(L)1). Taken together, these results suggest that ICT rechallenge may be associated with deep and durable benefit for certain patients.

Recent evidence has suggested that distinct mechanisms may be involved in antitumor immunity compared with irAEs, which may permit selective immunosuppression with steroid-sparing approaches and continuation of ICT.^{22,34,35} In one case of colitis treated with vedolizumab in our cohort, the patient achieved PR from SD after rechallenge, and the use of secukinumab enabled ICT treatment in a patient with psoriasis who achieved CR. Notably, this approach enabled ICT rechallenge after selected severe irAEs. Clinical trials investigating the role of targeted immunosuppression in irAEs are ongoing, including trials at our institution of infliximab, vedolizumab, and fecal microbiota transplantation in ICT-associated colitis (NCT04407247, NCT04038619). Furthermore, investigation into mechanisms of irAEs remains a highly active area of research to identify rational therapeutic targets and predictive biomarkers (eg, the presence of autoantibodies or clonally expanded peripheral T cells) to identify at-risk patients for early intervention.^{36–38}

The major strengths of our study are the inclusion of multiple tumor types (including urothelial carcinoma which has had less data on ICT rechallenge than RCC), comparable sample size to other major studies of ICT rechallenge, and detailed clinical information on severity (with the majority of cases being moderate and including a subset of severe cases), treatment (including selective immunosuppression), and outcomes (including duration of responses). We acknowledge that our study has several limitations, notably its retrospective nature and physician discretion regarding ICT discontinuation or rechallenge. As described above, the presence of irAEs alone in certain circumstances is associated with improved cancer outcomes; therefore, causality cannot necessarily be attributed to the ICT rechallenge. Due to the multiple factors contributing to the decision to discontinue versus rechallenge ICT, including differences in the distribution of irAEs (including type and grade) an accurate

comparison of clinical responses between the two groups is not feasible, outside of the context of a prospective clinical trial. This is particularly important in two patients, one of whom also received consolidative surgery (#59) and one whose first response assessment occurred after the development of the irAE (#13), which limits conclusions as to the benefit of ICT rechallenge in these two patients. Additionally, as irAEs were screened using specified search terms and subsequently confirmed by manual chart review, the reports rely on the accurate recording and documentation of irAEs by the treating physician. Finally, we did not have patients rechallenged with ICT who experienced toxicities that carry a particularly high mortality rate, such as myocarditis, myositis, and myasthenia gravis.

In conclusion, in this retrospective analysis of patients with genitourinary cancers (prostate, kidney, and bladder), ICT rechallenge after moderate-to-severe irAEs was associated with deep and durable responses in a subset of patients with RCC and UC, with an acceptable safety profile and no fatal events. Strategies to enable ICT resumption after moderate-to-severe irAEs, such as with targeted immunosuppression warrant further study.

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