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Safety and efficacy of restarting immune checkpoint inhibitors after clinically significant immune-related adverse events in metastatic renal cell carcinoma

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ABSTRACT

Background Immune checkpoint inhibitors (ICI) induce a range of immune-related adverse events (irAEs) with various degrees of severity. While clinical experience with ICI retreatment following clinically significant irAEs is growing, the safety and efficacy are not yet well characterized.

Methods This multicenter retrospective study identified patients with metastatic renal cell carcinoma treated with ICI who had >1 week therapy interruption for irAEs. Patients were classified into retreatment and discontinuation cohorts based on whether or not they resumed an ICI. Toxicity and clinical outcomes were assessed descriptively.

Results Of 499 patients treated with ICIs, 80 developed irAEs warranting treatment interruption; 36 (45%) of whom were restarted on an ICI and 44 (55%) who permanently discontinued. Median time to initial irAE was similar between the retreatment and discontinuation cohorts (2.8 vs 2.7 months, p=0.59). The type and grade of irAEs were balanced across the cohorts; however, fewer retreatment patients required corticosteroids (55.6% vs 84.1%, p=0.007) and hospitalizations (33.3% vs 65.9%, p=0.007) for irAE management compared with discontinuation patients. Median treatment holiday before reinitiation was 0.9 months (0.2–31.6). After retreatment, 50% (n=18/36) experienced subsequent irAEs (12 new, 6 recurrent) with 7 (19%) grade 3 events and 13 drug interruptions. Median time to irAE recurrence after retreatment was 2.8 months (range: 0.3–13.8). Retreatment resulted in 6 (23.1%) additional responses in 26 patients whose disease had not previously responded. From first ICI initiation, median time to next therapy was 14.2 months (95% CI 8.2 to 18.9) and 9.0 months (5.3 to 25.8), and 2-year overall survival was 76% (95%CI 55% to 88%) and 66% (48% to 79%) in the retreatment and discontinuation groups, respectively.

Conclusions Despite a considerable rate of irAE recurrence with retreatment after a prior clinically significant irAE, most irAEs were low grade and controllable. Prospective studies are warranted to confirm that retreatment enhances survival outcomes that justify the safety risks.

BACKGROUND

Dysregulation of immune checkpoint pathways, such as the programmed cell death-1 (PD-1) axis, is an important mechanism by which some tumors evade host immunity.[1] As of 2019, almost all patients with metastatic renal cell carcinoma (mRCC) will receive immune checkpoint inhibitors (ICI) targeting the PD-1 axis either alone or in combination with other ICI or vascular endothelial growth factor (VEGF) targeted therapies to re-engage cytotoxic T cells to destroy tumor cells. The anti-PD-1 antibody nivolumab improved overall survival compared with everolimus in the second-line treatment of patients with clear cell RCC after prior VEGF blockade, and more recently in combination with the anti-cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) antibody ipilimumab against sunitinib, for treatment-naïve mRCC.[2–4] In the past year, the treatment armamentarium has expanded to include two combination regimens that target both the VEGF and PD-1 pathways with the VEGFR tyrosine kinase inhibitor axitinib and the PD-1/L-1 inhibitors, pembrolizumab and avelumab. Two phase 3 trials with these combinations demonstrated significant benefits in objective response rate (ORR), progression-free survival (PFS), and in the case of pembrolizumab, overall survival compared with sunitinib.[5 6] Multiple other combination approaches employing an anti-PD-1/PD-L1 backbone are under investigation for both clear cell and non-clear cell histologies.

However, ICIs are associated with a unique class of adverse events, deemed immune-related adverse events (irAEs), related to their T-cell stimulating mechanism of

action.[7] Across the different agents and indications, the incidence of all grade irAEs varies from 15%–90% with monotherapy, with 6%–40% being grade ≥3.[2 3 6 8–11] Clinically significant irAEs requiring therapy discontinuation occur in 0.5%–13% of patients on ICI monotherapy and 22%–36% on dual ICI combinations such as nivolumab/ipilimumab.[2–4 9 12] In the phase 3 study of nivolumab plus ipilimumab in mRCC, 46% of patients developed grades 3–4 irAEs, with 35% requiring high-dose corticosteroids (≥40 mg prednisone or its equivalent) to manage the toxicity whereas in the phase 3 study of nivolumab monotherapy versus everolimus, 19% experienced grades 3–4 irAEs with nivolumab monotherapy.[3 4]

In general, management of moderate or severe irAEs requires ICI interruption and administration of immune-modulating medications such as corticosteroids and in some cases, more advanced immunosuppressants, such as mycophenolate mofetil or infliximab.[10 13–15] While recommendations for toxicity management have been developed from expert opinions of experienced investigators,[7 14 15] high-quality evidence to direct the optimal approach that might balance irAE control without counteracting antitumor efficacy is still lacking.

In addition, whether or not it is safe or necessary to resume checkpoint inhibition after a clinically significant irAE remains unclear. The literature is scarce regarding restarting ICI therapy after recovery from high-grade irAEs and is mostly derived from experiences in melanoma and non-small cell lung cancer (NSCLC), with no reported studies in RCC.[16–20] The overarching objective of this international, multicenter collaboration was to characterize the safety and efficacy of restarting ICI therapy after a clinically significant irAE, defined as one requiring treatment interruption or discontinuation, in patients with mRCC.

METHODS

Study design and participants

We designed a multicenter, retrospective cohort analysis of patients with mRCC treated with anti-PD-1/PD-L1 antibodies (eg, nivolumab, pembrolizumab, atezolizumab, avelumab, or durvalumab), as monotherapy or in combination with either anti-CTLA-4 therapy (eg, ipilimumab or tremelimumab), other investigational immunotherapy, or VEGF-targeted therapy. Eligible patients included those treated with an ICI who had a dose interruption for at least 1 week due to irAEs. Patients were classified into retreatment and discontinuation (no retreatment) cohorts based on whether or not they were subsequently retreated with ICI-based regimen after the resolution of the initial irAE. In patients with more than one treatment interruption due to an irAE, data collection and analysis were based on the first interruption. Patients who discontinued the ICI due to concomitant disease progression at the time of irAEs were excluded. Data were collected from two medical centers in the USA (Dana- Farber Cancer Institute (DFCI)/Brigham and Women's Hospital and Emory University Hospital) and one medical center in Canada (Tom Baker Cancer Centre).

Procedures

Institutional medical records were screened for patients with mRCC who had their ICI interrupted for >1 week due to a clinically significant irAE. A clinically significant irAE was defined as a new irAE during ICI treatment, which required dose interruption (with or without immunosuppressive therapy). All irAEs classes were captured, such as dermatological, gastrointestinal, hepatic, endocrine, rheumatological, neurological, cardiac, pulmonary and renal as per the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Data were collected based on each institution's existing Institutional Review Board approved protocols or waivers and were sent in a deidentified manner to the DFCI investigators, where the data were then pooled into a single secure database.

Outcomes

Safety was gauged based on the incidence of irAEs requiring treatment interruption. Toxicity was graded retrospectively using the CTCAE (version 5.0). Efficacy was assessed using parameters of duration of therapy (DOT), ORR, time to next therapy (TTNT), PFS, and overall survival. DOT was defined from the start of ICI therapy until permanent treatment discontinuation for any reason, or if still on treatment, the patient was censored at date of last follow-up. DOT included initial and, if occurred, retreatment periods. PFS was defined from the start of ICI therapy to disease progression or death from any cause or censored at date of last follow-up or on initiation of new therapy. TTNT was calculated as the interval from ICI initiation to institution of next therapy or death from any cause. Overall survival was defined from time of ICI initiation to death from any cause or censored at last follow-up. For the discontinuation cohort, we also explored treatment-free survival (TFS), defined as time from the last dose of ICI until disease progression, institution of next therapy or death from any cause, whichever came first, or censored at date of last follow-up. Response evaluation was investigator-assessed using response evaluation criteria in solid tumors principles (RECIST v1.1).[21]

Statistical analysis

Clinical and disease characteristics were summarized as median and range for continuous variables, and as number and percentage for categorical variables. The characteristics of patients and initial irAEs were compared between the retreatment and discontinuation groups by Fisher's exact test for categorical variables and Wilcoxon's rank sum test for continuous variables. The distributions of DOT, PFS, TTNT, TFS and overall survival were evaluated with the Kaplan-Meier methodology separately for each cohort. Since cohort assignment was based on treatment status after the initial irAE, and since there were inherent imbalances in physician or patient choice to re-treat or permanently discontinue ICI treatment, all

Table 1 Clinical and demographic characteristics of patient who had immune checkpoint inhibitor (ICI) interruption for immune-related adverse events.

Clinicodemographic characteristic	All patients (n=80)		Discontinuation (n=44)		Retreatment (n=36)		P value
	n/median	%/range	n/median	%/range	n/median	%/range	
Institution							0.91
DFCI	43	53.8%	23	52.3%	20	55.6%	
Emory	13	16.3%	8	18.2%	5	13.9%	
TBCC	24	30.0%	13	29.5%	11	30.6%	
Sex							0.99
Female	23	28.8%	13	29.5%	10	27.8%	
Male	57	71.3%	31	70.5%	26	72.2%	
Smoking							0.65
No	29	36.3%	17	38.6%	12	33.3%	
Yes	49	61.3%	26	59.1%	23	63.9%	
Missing	2	2.5%	1	2.3%	1	2.8%	
Age at ICI initiation	63.2	22.6–82.8	63.2	24.1–82.8	62.9	22.6–81.2	0.42
Histology							0.36
Clear cell	68	85.0%	39	88.6%	29	80.6%	
Non-clear cell	12	15.0%	5	11.4%	7	19.4%	
Differentiation							0.21
No	58	72.5%	32	72.7%	26	72.2%	
Sarcomatoid	19	23.8%	12	27.3%	7	19.4%	
Rhabdoid	2	2.5%	0	0.0%	2	5.6%	
Granular	1	1.3%	0	0.0%	1	2.8%	
ECOG performance status at ICI initiation							0.86
Missing	6	7.5%	3	6.8%	3	8.3%	
0	36	45.0%	21	47.7%	15	41.7%	
1	26	32.5%	14	31.8%	12	33.3%	
≥2	12	15.0%	6	13.6%	6	16.7%	
IMDC classification							0.22
Favorable	21	26.3%	11	25.0%	10	27.8%	
Intermediate	41	51.3%	26	59.1%	15	41.7%	
Poor	18	22.5%	7	15.9%	11	30.6%	
Line of ICI regimen							0.83
First line	40	50.0%	22	50.0%	18	50.0%	
Second line	27	33.8%	14	31.8%	13	36.1%	
Third line and above	13	16.3%	8	18.2%	5	13.9%	
Type of ICI							0.87
Monotherapy	35	43.8%	20	45.5%	15	41.7%	
Anti-PD-1/PD-L1 +VEGF-targeted therapy	19	23.8%	11	25.0%	8	22.2%	
Anti-PD-1/PD-L1 +anti-CTLA-4	23	28.8%	12	27.3%	11	30.6%	
Anti-PD-1/PD-L1 +other	3	3.8%	1	2.3%	2	5.6%	
Labs at baseline							
Free T4 (ng/dL)							0.22
N	58		32		26		
Median	1.3	0.22–9.7	1.3	0.73–9.7	1.3	0.22–7.9	

Continued

Table 1 Continued

Clinicodemographic characteristic	All patients (n=80)		Discontinuation (n=44)		Retreatment (n=36)		P value
	n/median	%/range	n/median	%/range	n/median	%/range	
TSH (U/mL)							0.33
N	72		43		29		
Median	2.2	0.01–77.15	2.1	0.12–23.16	2.21	0.01–77.15	
hemoglobin (g/L)							0.73
N	80		44		36		
Median	127	80–170	126.5	84–166	128	80–170	
Platelets (10^9/L)							0.21
N	80		44		36		
Median	246	70–866	258.5	129–866	230	70–703	
Absolute neutrophil count (K/UL)							0.26
N	80		44		36		
Median	4.5	1.56–13.8	4.9	1.76–12.36	4.1	1.56–13.8	
Absolute lymphocyte count (K/UL)							0.72
N	80		44		36		
Median	1.4	0.39–4.7	1.4	0.4–3.06	1.5	0.39–4.7	

DFCI, Dana-Farber Cancer Institute; PD-1, programmed cell death-1; TBCC, Tom Baker Cancer Centre; TSH, thyroid stimulating hormone; VEGF, vascular endothelial growth factor.

outcome analyses for the discontinuation and retreatment cohorts were descriptive in nature, with no formal comparisons between cohorts.

RESULTS

Characteristics of the study population

Of 499 patients with mRCC who had received ICI-based therapy in the metastatic setting between 2012 and 2019 at three institutions, 80 (16%) patients developed clinically significant irAEs necessitating drug interruption and met eligibility criteria (online supplementary figure 1). The majority were male (n=57, 71.3%) with good performance status (n=62, 77.5% Eastern Cooperative Oncology Group (ECOG 0–1) (table 1). Median age at ICI initiation was 63 years (range: 23–83 years). Most tumors were clear cell histology (n=68, 85.0%) with 19 (23.8%) having sarcomatoid differentiation. Half of the patients in our cohort had treatment-naïve disease (n=40, 50%). More than half (n=45, 56.3%) received ICIs in combination with VEGF-targeted therapy (n=19, 24%) or dual checkpoint inhibition with anti-CTLA-4 (n=23, 29%). The discontinuation cohort included 44 patients who permanently discontinued ICI treatment after the initial irAE whereas 36 patients who were restarted on ICIs after resolution of initial irAE comprised the retreatment cohort. The discontinuation and retreatment cohorts were balanced in terms of clinicodemographic characteristics including age, gender, histology, and international metastatic RCC database consortium (IMDC) risk categorization, among others (table 1).

Characteristics of initial irAEs

The distributions of the grades and classes of the initial irAEs were similar across the retreatment and discontinuation cohorts (table 2, online supplementary figure 2). Grade (G) 3/4 irAEs occurred in 26 (59.1%) and 17 (47.2%) patients in the discontinuation and retreatment groups, respectively (p=0.37). The most common irAEs requiring drug discontinuation were transaminitis (n=11, 25% vs n=5, 14%), colitis (n=10, 23% vs n=6, 17%), and pneumonitis (n=5, 11.4% vs n=3, 8.3%) in the discontinuation and retreatment cohorts, respectively. Rare but clinically significant irAEs of interest were encephalitis, myocarditis, peripheral neuropathy, and Steven-Johnson syndrome, occurring in one patient each within the discontinuation group and none of the retreatment patients (online supplementary table 1). Median time to development of the initial irAE was similar across the two cohorts: 2.7 (range: 0.4–74.7) and 2.8 (0.3–46.1) months in the discontinuation and retreatment cohorts, respectively (p=0.59). In terms of irAE management, a significantly higher number of discontinuation patients required steroids compared with the retreatment cohort (n=37, 84.1% vs n=20, 55.6%, p=0.007). While more than 90% of patients in both cohorts required systemic corticosteroids to manage the toxicities (n=36, 97.3% vs n=18, 90.0%, p=0.28), discontinuation patients required higher doses of steroids, defined as ≥40 mg prednisone or its equivalent (n=31, 83.8% vs n=10, 50.0%, p=0.01), and more frequent hospitalizations (n=29, 65.9% vs n=12, 33.3%, p=0.007; table 2). Of the 11 patients who required

Table 2 Characteristics of initial immune-related adverse events (irAEs)

	Discontinuation (n=44)		Retreatment (n=36)		
	N/median	%/range	N/median	%/range	P value
Type of irAE					
Elevated AST/ALT	11	25.0%	5	13.9%	
Colitis	10	22.7%	6	16.7%	
Pneumonitis	5	11.4%	3	8.3%	
Skin	3	6.8%	5	13.9%	
Elevated lipase	2	4.6%	5	13.9%	
Adrenal insufficiency	2	4.6%	2	5.6%	
Hypophysitis	2	4.6%	3	8.3%	
Nephritis	2	4.6%	1	2.8%	
Arthritis	1	2.3%	3	8.3%	
Encephalitis	1	2.3%	0	0.0%	
Hypothyroidism	1	2.3%	1	2.8%	
Myocarditis	1	2.3%	0	0.0%	
Other	1	2.3%	1	2.8%	
Peripheral neuropathy	1	2.3%	0	0.0%	
Polymyalgia rheumatica	1	2.3%	0	0.0%	
Type 1 diabetes	0	0.0%	1	2.8%	
Grade of irAE					0.37
G1/2	18	40.9%	19	52.8%	
G3/4	26	59.1%	17	47.2%	
Hospitalization*					**0.007**
No	15	34.1%	24	66.7%	
Yes	29	65.9%	12	33.3%	
Any steroid use (local or systemic)*					**0.007**
No	7	15.9%	16	44.4%	
Yes	37	84.1%	20	55.6%	
Systemic steroid use					0.28
No	1	2.7%	2	10.0%	
Yes	36	97.3%	18	90.0%	
Systemic steroid use ≥40 mg*					**0.01**
No	6	16.2%	10	50.0%	
Yes	31	83.8%	10	50.0%	
Duration of steroid course >4 weeks					0.64
No	4	10.8%	1	5.0%	
Yes	33	89.2%	19	95.0%	
Additional line of immunosuppression					0.37
No	40	90.9%	35	97.2%	
Yes	4	9.1%	1	2.8%	
Time to irAE onset, mos	2.7	0.4–74.7	2.8	0.3–46.1	0.59
Therapy interruption before retreatment, mos	NA	NA	0.9	0.2–31.6	

*p-value<0.05.
ALT, alanine transaminase; AST, aspartate transaminase; mos, months.

steroid reinitiation for irAE flare after taper, 9 (81.8%) were discontinuation patients. Five patients required additional immunosuppressive therapy beyond steroids to manage their irAEs, including four discontinuation patients and one retreatment patient. No toxicity-related deaths were observed in either cohort.

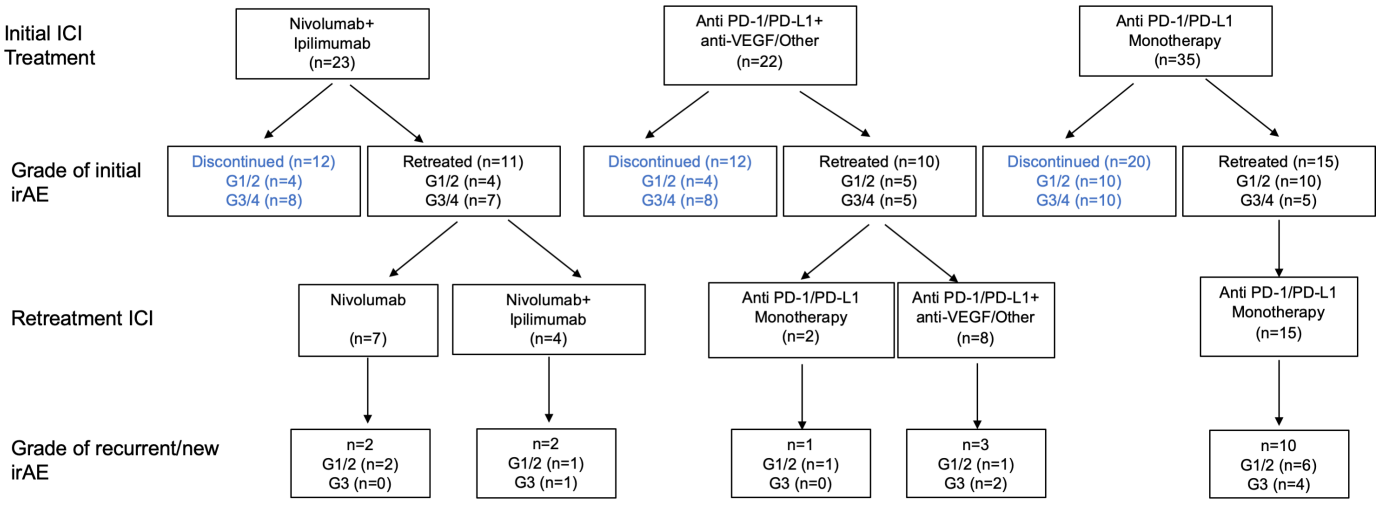


Figure 1 Grade of immune-related adverse event (irAE) according to the type of immune checkpoint inhibitor (ICI) at the initial and retreatment stages. PD-1, programmed cell death-1; VEGF, vascular endothelial growth factor

Clinical features of patients with latent initial irAEs

Given the wide time range during which patients in both cohorts developed the initial irAEs (median: 2.8 months; range 0.3–74.7), we also characterized latent irAEs, defined here as irAEs that initially developed 12 months after starting ICI therapy. Of 10 patients who developed latent irAEs, 3 were receiving combination therapy and 7 were treated with anti-PD-1/PD-L1 monotherapy. G3 irAEs occurred in four patients and G1/2 irAEs in six patients. Systemic steroids were administered in five cases, and two patients required hospitalization for management of the initial irAEs. Half of the patients (n=5/10) were restarted on ICIs.

Clinical features of initial irAEs in patients on combination therapy

Across different ICI types, there were more G3/4 irAEs in patients on a combination regimen compared with patients on ICI monotherapy (anti-PD-1/PD-L1 +anti-CTLA-4: n=15/23, 65%; anti-PD-1/PD-L1 +anti-VEGF/other: n=13/22, 59%; anti-PD-1/PD-L1 monotherapy: n=15/35, 43%). Among those who initially received anti-PD-1/PD-L1 +anti-CTLA-4 (all nivolumab +ipilimumab, n=23), 11 were rechallenged. Most switched to nivolumab alone (n=7, 63.5%) while four patients (36.3%) were restarted on the combination. Of these 11 patients, 7 (63.6%) had G3/4 irAEs initially. It did not appear that the initial grade of irAE predicted whether the patient would be rechallenged with monotherapy or combination. Of the patients with initial G3/4 irAEs, 42.9% (n=3/7) patients were restarted on the combination. On the contrary, only one of four patients (25.0%) with initial low-grade irAEs (G1/2) was restarted on the combination. Of 22 patients who were initially treated with anti-PD-1/PD-L1 +anti-VEGF/other therapy, 10 were rechallenged; the majority (n=8/10) were retreated with the same combination (figure 1).

Safety of retreatment with ICIs after initial irAEs

Of the 36 patients who were restarted on ICIs after drug interruption due to irAE, median time off therapy was 0.9 months (range: 0.2–31.6 months). At the time of ICI retreatment, the initial irAEs had resolved completely in 55.6% of patients (n=20). In 30.6% (n=11) and 13.9% (n=5) of patients, their irAEs had resolved to G1 and G2, respectively. Half of the 36 patients (n=18, 50%) developed another irAE. Two-thirds (n=12) experienced a new type of irAE, and one-third (n=6) experienced the same irAE. Median time to development of a recurrent or new irAE was 2.8 months (range: 0.3–13.8 months). All irAEs that occurred after retreatment were grade ≤3 with no grade 4 or 5 events. Six patients (33.3%) required hospitalization, and 11 (61.1%) required systemic steroids for symptom management (table 3; online supplementary figure 3).

Of the 18 patients who experienced another irAE, 13 patients required therapy interruption for at least 1 week due to the new/recurrent irAE. Of those, 10 patients permanently discontinued treatment, and 3 patients were restarted on the same ICI-based regimen. Two of the latter three patients developed a second recurrence (same irAE): a grade 3 colitis necessitating hospitalization for intravenous steroids and a grade 2 dermatitis requiring oral steroids. Both permanently discontinued ICI due to the second irAE recurrence. No grade 4 or 5 events were observed after the second irAE.

Characteristics of patients with recurrent irAEs

Delving into the baseline characteristics of the 18 patients who developed recurrent/new irAEs, the majority had G1/2 irAEs initially (n=11/18, 61.1%). Five patients required hospitalization and nine patients received steroids for management of the initial irAE. Most patients with recurrent/new irAEs (n=17/18, 94.4%) developed their initial irAE within 1 year of ICI initiation whereas one patient (n=1/18) had a latent irAE. The patient

Table 3 Characteristics of the immune-related adverse events (irAEs) after immune checkpoint inhibitor rechallenge (retreatment cohort n=36)

	N	%
Recurrent irAE	**6**	
Colitis	2	5.6%
Dermatological	2	5.6%
Elevated lipase (symptomatic)	1	2.8%
Pneumonitis	1	2.8%
New irAE	**12**	
Colitis	2	5.6%
Transaminitis	2	5.6%
Hypothyroidism	2	5.6%
Pneumonitis	2	5.6%
Dermatological	1	2.8%
Adrenal insufficiency	1	2.8%
Anemia	1	2.8%
Arthritis	1	2.8%
Recurrent/new irAE grade		
G1/2	11	30.6%
G3	7	19.4%
Management of recurrent irAE (evaluable n=18)		
Hospitalization		
No	12	66.7%
Yes	6	33.3%
Steroid use and modality		
No use	6	33.3%
Local	1	5.6%
Systemic	11	61.1%
Duration of any steroid course		
No use	6	33.3%
≤4 weeks	1	5.6%
>4 weeks	11	61.1%
Drug interruption for ≥1 week		
No	5	27.8%
Yes	13	72.2%
Retreatment following second drug interruption		
No (permanent discontinuation)	10	76.9%
Yes	3	23.1%

with the latent irAE also experienced a latent recurrent G1 colitis 14 months after retreatment, which did not require hospitalization or steroid use. The grade of the recurrent/new irAE according to the type of ICI at the initial and retreatment stages is summarized in figure 1.

For the seven patients who developed recurrent G3 irAEs, n=2/7 had prior G3 irAEs, whereas n=5/7 had a prior G1/G2 irAE. For the 11 patients with lower grade (G1/G2) irAE recurrences, the spectrum of initial irAE grades was G2 (n=6/11), G3 (n=2/11), or G4 (n=3/11; online supplementary figure 3).

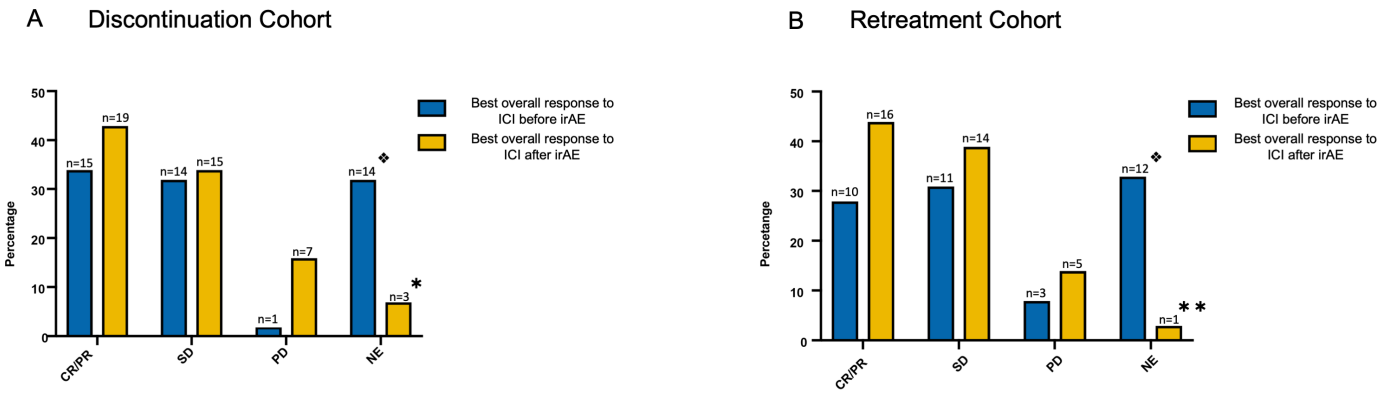
Efficacy outcomes on ICI

Median follow-up time from ICI initiation was 23.2 months (range: 4.9–85.4) for the whole cohort. Median DOT from ICI initiation was 2.5 months (range: <1.0–73.7) for the discontinuation cohort and 10.6 months (range: 1.6–68.2) for the retreatment cohort. For patients who resumed ICI, median time on therapy after retreatment was 5.3 months (range: <1.0–21.3). Thirty-two (89%) patients had permanently discontinued ICI in the retreatment group at last follow-up (Supplementary figure 1).

At the time of initial irAE, ORR was 34% (n=15/44) in the discontinuation cohort and 28% (n=10/36) in the retreatment cohort, with 14 (32%) and 12 (33%) patients non-evaluable, respectively (figure 2). Retreatment resulted in 6 (23.1%) new PRs in the 26 retreatment patients, whose disease had not responded prior to the temporary drug interruption. Of the 29 discontinuation patients who had not achieved a response prior to permanent discontinuation, 4 (13.8%) experienced a subsequent PR off therapy before starting next therapy. Overall, the best ORR at any time (on initial therapy, after ICI reinitiation, or after discontinuation but before next therapy) was 44% (95% CI 28% to 62%) and 43% (95% CI 28% to 59%) in the retreatment and discontinuation cohorts, respectively (figure 2; table 4).

For the retreatment cohort, median PFS and TTNT from initial ICI initiation was 13.2 months (95% CI 7.7 to 21.9) and 14.2 months (95% CI 8.2 to 18.9), respectively. Median overall survival from initial ICI initiation was not reached. Two-year overall survival rate was 76% (95% CI 55% to 88%; figure 3 and table 4).

For the discontinuation cohort, median TTNT from ICI start was 9.0 months (95% CI 5.3 to 25.8). Median PFS could not be reliably assessed in this cohort given a large proportion of patients (30%, n=13/44) had started next therapy before progressing after ICI discontinuation. The 2-year overall survival rate from initial ICI initiation was 66% (95% CI 48% to 79%; table 4 and figure 3). The 1-year TFS survival from ICI discontinuation was 37% (95% CI 23% to 51%), with 10 patients remaining progression/treatment free at 1 year off therapy (online supplementary figure 4). Of the 10 patients with sustained disease control at least 1 year off therapy, most had good performance status (n=9 with ECOG PS 0 or 1). Three patients had good risk disease, and seven patients had intermediate risk disease by IMDC criteria. Median time to initial irAE in this group was 7.4 months (range: 2.6–19.8). At the time of irAE, four patients had complete or partial response to ICIs, and six patients had stable disease. Of these 10 patients, six experienced G3/4 irAEs requiring hospitalization, and nine patients received steroids for toxicity management.



❖ At the time of the irAE in question, n=14 and n=12 patients from the discontinuation and retreatment cohorts respectively did not have response scans available, as the irAE took place before the first scan for response assessment was done

✱ After irAE, three patients from the discontinuation cohort did not have response assessment scans as these patients were taken off drug, with no scans done prior to start of next therapy

✱ ✱ No scans were available for one patient in the retreatment cohort

Figure 2 Response to immune checkpoint inhibitors (ICIs) for patients in the discontinuation and retreatment cohorts. (A) Best response achieved prior to immune-related adverse event (irAE) and the best overall response to ICI in the discontinuation cohort. (B) Best response achieved prior to irAE and best overall response to ICI in the retreatment cohort. CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

DISCUSSION

In this retrospective, multicenter study, we shed light on the safety and efficacy of restarting patients on ICIs after discontinuation for clinically significant irAEs, in the largest reported mRCC cohort to our knowledge. Rechallenging patients with ICIs after discontinuation for toxicity resulted in another irAE (new or recurrent) in 50% of patients with mRCC, which was similar to published data from small series in melanoma, NSCLC, lymphoma and other solid tumors (50%–55%).[17–19] However, these irAEs appear to be manageable with no grade 4 toxicity or treatment-related deaths in our experience. Clinicians were no doubt more vigilant about toxicity monitoring in patients retreated with ICIs, and, in our study, tended to discontinue therapy on new or recurrent onset of irAEs after retreatment (72.2%), irrespective of the irAE grade.

Table 4 Treatment outcomes with immune checkpoint inhibitors (ICI)

	Discontinuation (n=44)	Retreatment (n=36)
Overall ORR (95% CI) *	43% (28% to 59%)	44% (28% to 62%)
TTNT from initial ICI start		
No. of events	29	27
Median, mos (95% CI)	9.0 (5.3 to 25.8)	14.2 (8.2 to 18.9)
PFS from initial ICI start		
No. of events	NE†	26
Median, mos (95% CI)	NE†	13.2 (7.7 to 21.9)
OS from initial ICI start		
No. of deaths	15	12
One-year OS rate (95% CI)	81% (66% to 90%)	89% (73% to 96%)
Two-year OS rate (95% CI)	66% (48% to 79%)	76% (55% to 88%)

*Overall objective response rate (ORR)=best response at any time (initial treatment, after permanent discontinuation, or after retreatment).
†Not evaluable (NE) as 30% of patients in the discontinuation group started on a new therapy prior to progression after ICI discontinuation.
OS, overall survival; PFS, progression-free survival; TTNT, time to next therapy.

Unless contraindicated, most patients with mRCC will receive ICI as part of the first-line regimen.[22 23] Despite its retrospective nature, this effort addresses a critical unresolved question that clinicians face in the clinic, for mRCC and across other solid tumors in which immune checkpoint blockade is standard treatment or is being investigated. It is crucial to understand the safety aspects of retreatment and to prove that doing so actually provides additional benefit in terms of prolonged disease control, enhanced quality of life, and/or improved survival. Most of the published data are derived from small series of the melanoma and NSCLC, or focuses only on one irAE of interest such as colitis.[16–20 24] Data are lacking in the mRCC space, where ICI-based therapy is now standard of care.

In our study, retreatment patients tended to have relatively milder initial irAEs, usually necessitating fewer steroid requirements and fewer hospitalizations. Indeed, when faced with more severe irAEs, ICI discontinuation is expected, as many clinicians would be hesitant to restart the ICI in this setting given the absence of safety and efficacy data supporting retreatment. Our findings are in accordance with the NSCLC experience of 68 patients, where retreated patients tended to have less severe and more manageable irAEs.[18] In our series, the median time to development of an irAE after restarting ICI therapy was similar to the median time to initial irAE onset at

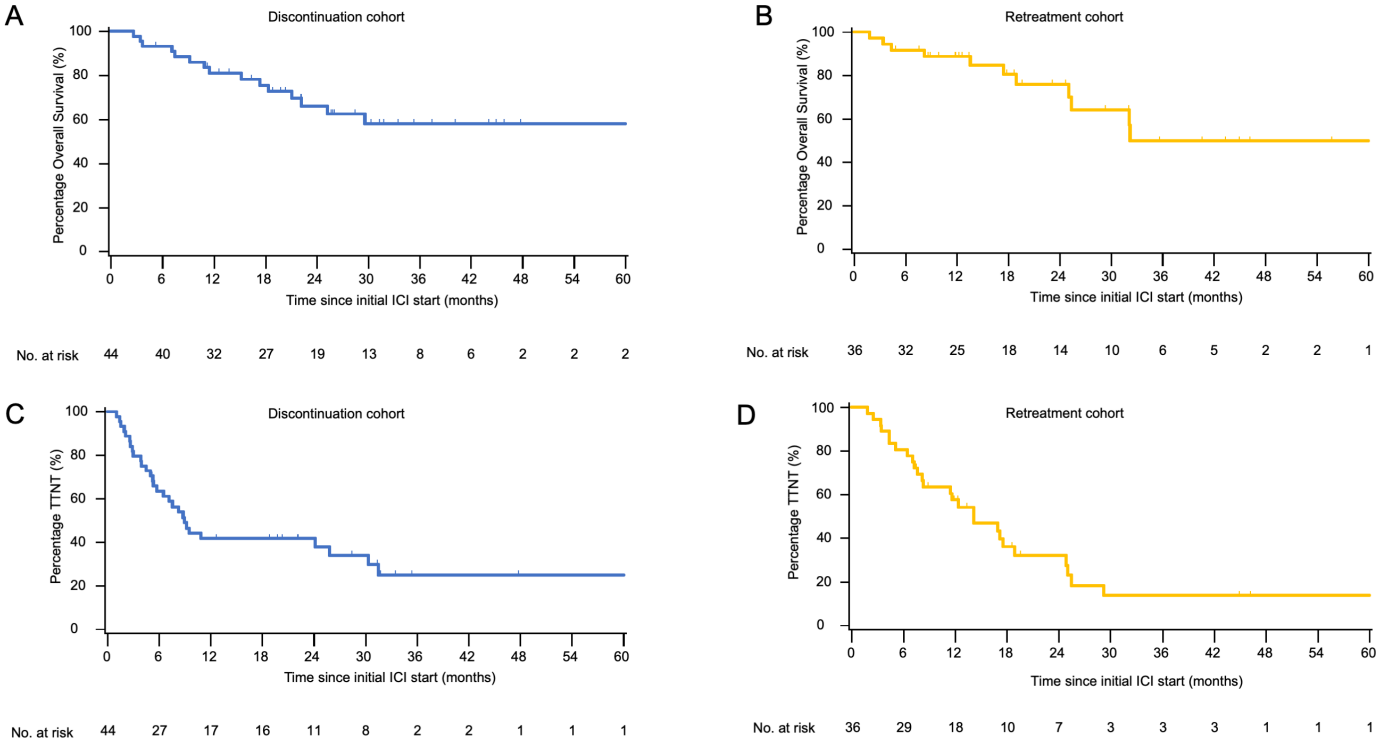


Figure 3 Kaplan-Meier curves for overall survival and time to next therapy (TTNT). (A) Overall survival in the discontinuation cohort. (B) Overall survival in the retreatment cohort. (C) TTNT in the discontinuation cohort. (D) TTNT in the retreatment cohort. ICI, immune checkpoint inhibitor.

approximately 3 months. In the majority of cases, new or recurrent irAEs tended to be less severe than the initial irAE suggesting that the severity of the initial irAE may not be predictive of the severity of irAE recurrence. We did not observe any retreatment-related deaths, with median time on ICI therapy of 5.7 months after reinitiation. Conversely, the risk of experiencing a third exacerbation after a second drug holiday was high at 67% (n=2/3); however, the small numbers limit conclusions. With respect to latent irAEs (development >1 year after ICI initiation), we observed a trend that patients with latent irAEs, who were retreated with ICIs generally had a favorable ICI toxicity profile. Of these patients, 20% experienced a recurrent irAE that was mild (ie, grade 1, no steroid requirement or hospitalization). This finding that latent irAEs may be associated with preferable safety outcomes for patients on rechallenge is hypothesis generating but given the small cohort size, these observations must be interpreted carefully.

The risk of subjecting a patient to a recurrent or new clinically significant irAE should only be considered in the pursuit of increased efficacy. There is evidence supporting enhanced efficacy of ICI therapy in patients who develop more clinically significant irAEs,[25–27] but it is unknown whether retreatment after an initial irAE enhances disease control further. The argument against rechallenge is that patients may continue to have response or durable disease control even when stopping therapy after an irAE.[28 29] In our study, restarting patients on ICI resulted in six PRs (23.1%) in disease which had not responded prior to irAE, whereas four subsequent PRs (13.8%) were observed off therapy in the discontinuation cohort. A similar rate of subsequent PRs was reported in patients with NSCLC after restarting ICI (19.2%, n=5/26).[18] Furthermore, our work shows that the median PFS in the retreatment cohort was 13.2 months (95% CI 7.7 to 21.9), comparable to published data from the treatment-naive anti-PD-1/L1 plus axitinib combination phase three trials.[5 6] In our series, TTNT was longer in the retreatment cohort compared with the discontinuation cohort, with the caveat that 30% of discontinuation patients were started on next line without progression compared with 8% of the retreatment patients. However, in our discontinuation cohort, at the time of the initial irAE, 10 patients had sustained disease control off therapy for at least 1 year, which could provide support for halting therapy rather than rechallenge. These findings, in addition to other inherent biases among the two cohorts in terms of physician and/or patient choice to retreat with ICI after clinically significant irAE, prevented direct statistical comparison on any survival outcomes (TTNT, PFS or 2 year OS) between the two cohorts.

The main limitation of our study is its retrospective nature and physician subjectivity in terms of which patients were selected for retreatment versus permanent discontinuation. As such, analysis of clinical outcomes was descriptive without formal comparison between cohorts even though the two cohorts were very similar in their baseline characteristics that are known to be prognostic such as IMDC risk criteria. Despite its imperfections, retrospective data can be helpful to conceptualize the real spectrum of treatment toxicity and its varied management.

CONCLUSIONS

In conclusion, our work highlights this knowledge gap in the field and the need to catalogue our collective experiences to provide real-world evidence as we await prospective studies. Currently, clinical decisions are driven more by physician experience and comfort rather than high-level evidence. While the absolute clinical benefit in terms of overall survival remains uncertain, our findings suggest that select patients with mRCC may safely be retreated with ICIs after initial irAEs. Despite an appreciable rate of recurrence, less than 20% of irAEs were grade 3, and no grade 4 or 5 events were observed, but conclusions are limited by the retrospective scope of this study. These results contribute to the growing literature that can guide retreatment with ICIs in RCC, and across the range of malignances where checkpoint inhibitors are now standard of care. Our work and that of others underscore the need for more standardized recommendations and prospective studies to confirm the safety of ICI reinitiation and to evaluate whether reinitiation translates to prolonged survival. In the interim, when considering ICI rechallenge, tailoring of therapy and careful discussion with the patient with early inclusion of a multidisciplinary team and vigilant monitoring is recommended to optimize care to the individual patient.

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