Research Article

Cancer Immunology Research

Durable Clinical Benefit in Metastatic Renal Cell Carcinoma Patients Who Discontinue PD-1/PD-L1 Therapy for Immune-Related Adverse Events

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Abstract

The current standard of care for treatment of metastatic renal cell carcinoma (mRCC) patients is PD-1/PD-L1 inhibitors until progression or toxicity. Here, we characterize the clinical outcomes for 19 mRCC patients who experienced an initial clinical response (any degree of tumor shrinkage), but after immune-related adverse events (irAE) discontinued all systemic therapy. Clinical baseline characteristics, outcomes, and survival data were collected. The primary endpoint was time to progression from the date of treatment cessation (TTP). Most patients had clear cell histology and received anti–PD–1/PD-L1 therapy as second-line or later treatment. Median time on PD-1/PD-L1 therapy was 5.5 months (range, 0.7–46.5) and median TTP was 18.4 months (95% CI, 4.7–54.3) per Kaplan–Meier estimation. The irAEs included arthropathies, ophthalmopathies, myositis, pneumonitis, and diarrhea. We demonstrate that 68.4% of patients ($n = 13$) experienced durable clinical benefit off treatment (TTP of at least 6 months), with 36% ($n = 7$) of patients remaining off subsequent treatment for over a year after their last dose of anti–PD-1/PD-L1. Three patients with tumor growth found in a follow-up visit, underwent subsequent surgical intervention, and remain off systemic treatment. Nine patients (47.4%) have ongoing irAEs. Our results show that patients who benefitted clinically from anti–PD-1/PD-L1 therapy can experience sustained beneficial responses, not needing further therapies after the initial discontinuation of treatment due to irAEs. Investigation of biomarkers indicating sustained benefit to checkpoint blockers are needed. *Cancer Immunol Res; 6(4); 402–8. ©2018 AACR.*

Introduction

Tumor cells have many mechanisms by which they can evade surveillance by the immune system. Immune checkpoints, such as CTLA-4 and PD-1, have been implicated in tumor evasion (1). When the PD-1 protein, expressed on T cells, binds to its ligands, PD-L1 or PD-L2, expressed on cancer cells and other cells in the tumor microenvironment, it acts as a negative regulator of the immune response (2–4). Monoclonal antibodies (mAb) that target and block PD-1 and PD-L1 interactions inhibit tumor evasion and enhance the host's immune response against the tumor. These mAbs have demonstrated efficacy in the treatment of an expanding list of malignancies, such as melanoma, non–small cell lung cancer (NSCLC), renal cell carcinoma (RCC), head and neck squamous cell carcinoma, and urothelial carcinoma (1, 5–17). With the FDA's approval of now five PD-1/PD-L1 inhibitors (atezolizumab, pembrolizumab, nivolumab, avelumab, and durvalumab) in multiple cancers (18), and more agents in development, PD-1/PD-L1 inhibitors are being increasingly utilized in clinical practice and have a favorable tolerability profile.

Nivolumab has been approved as a second-line treatment option for mRCC patients who have progressed on vascular endothelial growth factor (VEGF)–targeted therapies (11). It is typically given until disease progression or development of intolerable toxicities. However, evidence supporting the need to continue PD-1/PD-L1 inhibitors is lacking. The "memory" component of the immune response and the ability of these agents to reset the equilibrium between the tumor and the host immune response support the hypothesis of a possible persistent, clinical benefit even after treatment discontinuation, and even if a complete response was not achieved (19, 20).

PD-1/PD-L1 inhibitors are associated with a unique spectrum of toxicities suspected to be due to immune system overactivation and termed immune-related adverse events (irAE). These toxicities more commonly occur in the gastrointestinal system, lungs, and skin, but any organ system can be at risk (21). They are usually treated with corticosteroids and rarely immune modulating agents. In RCC, treatment discontinuation for irAEs was observed in 8% of the patients (11). In melanoma, studies have shown that

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the development of irAEs is associated with a response to immune-checkpoint blockade (22, 23), but no studies have specifically evaluated the association between efficacy and irAEs in RCC. We sought to evaluate the clinical outcomes of mRCC patients who discontinued treatment with PD-1/PD-L1 inhibitors due to irAEs after initially experiencing a clinical response to therapy. Our results contribute data on whether prolonged continuous use of PD-1/PD-L1 is necessary for mRCC patients to derive durable clinical benefit.

Materials and Methods

Study design and patients

We conducted an analysis of mRCC patients treated at five academic institutions: Dana-Farber Cancer Institute, Massachusetts General Hospital, and Beth Israel Deaconess Medical Center in Boston, MA, as well as the Hospital Universitario 12 de Octubre in Madrid, Spain, and Beneficencia Portuguesa de Sao Paulo in Sao Paulo, Brazil. Eligible patients included those who discontinued therapy by the treating physician given the development of an irAE after initially having a clinical response/benefit to treatment with a PD-1 or PD-L1 inhibitor. Clinical response/benefit was defined as a complete response (CR) or partial response (PR), using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria, or stable disease (SD), as defined by RECIST version 1.1, if associated with tumor shrinkage. Patients were assessed by imaging assessments at varying time points based on investigator discretion. Clinical characteristics, response, and survival data were extracted from the electronic medical records. The immune-related toxicities were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Investigator discretion was used as the discontinuation criteria for all patients. All patients provided written informed consent for publication of their individual clinical information in this study.

Statistical analysis

Clinical and disease characteristics were summarized as medians and ranges for continuous variables and as numbers and percentages for categorical variables. Time-on treatment was calculated from the date of the first dose of PD-1/PD-L1 inhibitor therapy to the date of the last dose of PD-1/PD-L1 inhibitor therapy for patients receiving monotherapy, or, for patients receiving combination therapy of a PD-1/PD-L1 inhibitor with another agent, the date of the last dose of both agents. Time-to-progression (TTP) from the date of treatment cessation was calculated as the date of discontinuation of the PD-1/PD-L1 regimen to the date of initiation of subsequent systemic therapy, date of resection of a progressing metastatic lesion, date of decision to transition to best supportive care (BSC), death, or most recent follow-up, whichever came first.

Results

Baseline characteristics

Our cohort included 19 patients with mRCC who had a clinical response to anti–PD-1/PD-L1 therapy and subsequently discontinued treatment secondary to irAEs. The median age of the cohort was 68 years (range, 24–79; Table 1). Most patients had clear cell histology ($n = 18$, 94.7%). Among the patients with clear cell RCC, 3 patients had sarcomatoid features (15.8%). Four patients (21.1%) had liver metastases, and 3 (15.8%) had bone metastases. Most patients had a prior nephrectomy ($n = 18$, 94.7%). Five patients (26.3%) had International mRCC Database Consortium (IMDC) poor-risk disease.

Treatment exposure

Eleven patients (57.9%) were previously treated, and eight (42.1%) received a PD-1 inhibitor in the second-line setting. Ten patients (52.6%) were treated with VEGF tyrosine kinase inhibitors (TKI) before PD-1/PD-L1–targeted therapy.

Most patients received anti–PD-1 therapies ($n = 15$, 78.9%), with only 4 patients treated with anti–PD-L1 therapies (21.1%). Twelve patients (63%) received anti–PD-1/PD-L1 treatment as monotherapy and 7 (36.8%) patients received them in combination with other systemic therapies, including 4 patients (21.1%) receiving VEGF-targeted therapy and 3 (15.8%) CTLA-4 blockade. Overall, the median time-on PD-1/PD-L1 therapy was 5.5 months (range, 0.7–46.4 months; Table 2).

Table 1. Patient and disease characteristics

ID	Age (y)	Gender	Histology	Bone mets	Liver mets	IMDC risk group	Prior nephrectomy
1	68	M	Clear cell	No	Yes	Intermediate	Yes
2	66	M	Clear cell, sarcomatoid features	No	No	Intermediate	Yes
3	59	M	Clear cell	No	No	Poor	Yes
4	69	M	Clear cell	No	No	Favorable	Yes
5	24	M	Translocation	No	No	Intermediate	Yes
6	59	M	Clear cell	Yes	No	Poor	No
7	72	M	Clear cell, sarcomatoid features	Yes	No	Poor	Yes
8	68	F	Clear cell	No	No	Favorable	Yes
9	75	M	Clear cell, with chromophobe features	No	Yes	Favorable	Yes
10	75	M	Clear cell	Yes	No	Poor[a]	Yes
11	68	M	Clear cell	No	No	Intermediate	Yes
12	77	F	Clear cell	No	Yes	Intermediate	Yes
13	68	M	Clear cell	No	No	Intermediate	Yes
14	79	M	Clear cell	No	No	Intermediate	Yes
15	75	F	Clear cell	No	Yes	Intermediate[a]	Yes
16	68	F	Clear cell	No	No	Favorable	Yes
17	66	F	Clear cell, sarcomatoid features	No	No	Intermediate	Yes
18	65	M	Clear cell	No	No	Poor	Yes
19	66	M	Clear cell	No	No	Intermediate	Yes

Abbreviations: M, male; F, female, Mets, metastasis; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.
[a]IMDC risk group determined at the start of anti–PD-1/PD-L1 therapy due to lack of clinical information regarding the IMDC prognostic criteria at diagnosis.

Table 2. Treatment exposure and outcomes

ID	Line of anti–PD-1/PD-L1 therapy	Prior therapy	Anti–PD-1/PD-L1 therapy	Time on therapy (Mos)	Best response	TTP from the date of treatment cessation (Mos)	Subsequent therapy (best response)
1	1	N/A	PD-L1+	2.7	PR	1.4	Cabozantanib (PR)
2	3	Gemcitabine + sutent (VEGF TKI), sutent	PD-1	3.8	PR	3	Cabozantanib (PR)
3	3	Sutent + angiopoetin inhibitor, temsirolimus (mTOR inhibitor) +avastin (VEGF mAb)	PD-1	3.7	PR	3.4	Axitinib (SD, 17% growth), sorafenib (NE), pazopanib (NE)
4	1	N/A	PD-L1+	0.7	SD, 9% shrinkage	4.5[a]	BSC, pazopanib (TBD)
5	2	Sutent	PD-1	4.1	PR	4.7	Cabozantanib (SD, 15% shrinkage)
6	1	N/A	PD-L1+	2.7	PR	5.6	Cabozantanib (SD, 9% shrinkage), axitinib (TBD)
7	2	Sutent	PD-1	1.8	PR	7.4[b]	N/A
8	1	N/A	PD-1+	10.2	SD, 15% shrinkage	7.8[b]	N/A
9	2	Sutent	PD-1	6	SD, 4% shrinkage	8.2	N/A
10	6	Sutent, axitinib (VEGF TKI), everolimus (mTOR inhibitor), pazopanib, sutent	PD-1	6.1	SD[c]	9.5	N/A
11	1	N/A	PD-1+	8.8	CR	10.1	N/A
12	2	Axitinib	PD-1	5.5	SD, 1% shrinkage	10.6	N/A
13	1	N/A	PD-1+	4.6	PR	17.5	N/A
14	2	Sunitinib + angiopoetin inhibitor	PD-L1	7	SD, 10% shrinkage	18.4	Pazopanib (SD, 11% growth)
15	2	Sunitinib	PD-1	46.5	PR	22.8	N/A
16	1	N/A	PD-1+	3.8	PR	26.7	N/A
17	2	Pazopanib	PD-1	15.7	PR	29.1	N/A
18	1	N/A	PD-1	11.7	CR	48.7	N/A
19	2	Interleukin-2	PD-1	11.8	SD[c]	54.3[b]	N/A

Abbreviations: N/A, not applicable as patient remains progression-free; PD-1^{+}, anti–PD-1 combination therapy, PD-1, anti–PD-1 monotherapy; PD-L1, anti–PD-L1 monotherapy; PD-L1^{+}, anti–PD-L1 combination therapy; Mos, months; SD, stable disease with tumor shrinkage; CR, complete response; PR, partial response; TBD, to be determined; BSC, best supportive care; OS, overall survival.

[a]TTP from the date of treatment cessation stopped at time of transition to best supportive care.

[b]TTP from the date of treatment cessation for this patient stopped at the time of progressing metastatic lesion. These patients developed tumor growth in isolated areas treated with surgical intervention only. NE, not evaluable; VEGF, vascular endothelial growth factor; TKI, tyrosine kinase inhibitor; mTOR, mechanistic target of rapamycin; mAb, monoclonal antibody.

[c]% change not available.

Treatment-related toxicities

Nine (47.4%) patients had grade 2, 10 (52.6%) had grade 3, and 3 (15.8%) patients had grade 4 irAEs. The toxicities included arthropathies (n = 5, 26.3%), ophthalmopathies (uveitis, iritis, blepharitis), hypophysitis, myositis, pneumonitis, pruritus, pericarditis/myocarditis, acute interstitial nephritis, hepatitis, amylase/lipase elevation, and diarrhea (Table 3). Nine patients (47.4%) had ongoing irAEs at the time of last follow-up; 6 irAEs had been ongoing for over a year.

Most patients (n = 16, 84.2%) were treated with corticosteroids for irAEs. At time of analysis, 5 patients required ongoing corticosteroids (range, 12.7–48.1 months) and 11 patients were able to discontinue corticosteroids treatment (range, 0.5–4.8 months). Three patients received additional immunologic agents: 1 received methotrexate (a dihydrofolate reducatase inhibitor), 1 methotrexate in combination with chloroquine (an antimalarial agent) for arthralgias, and another received infliximab (an antibody against tumor necrosis factor-α) and intravenous immunoglobulin for autoimmune myocarditis. One patient with joint pain switched to methotrexate due to corticoteroids-related side effects, but required the addition of a lower dose of steroids 7 months later for more effective treatment of toxicities. Another patient began treatment with chloroquine and methotrexate in addition to prednisone. This patient's symptoms improved significantly, but the patient has been unable to taper off steroids. Three patients were not treated with immune modulating drugs: 1 did not receive treatment for asymptomatic amylase/lipase elevations, 1 received colchicine (microtubule inhibitor) for autoimmune pericarditis, and 1 received diphenhydramine (antihistamine) for treatment of severe pruritus. No deaths were attributed to irAEs.

Outcomes

The median time on anti–PD-1/PD-L1 therapy was 5.5 months (range, 0.7–46.5), with most patients on treatment for <6 months (n = 10, 52.6%). Two patients (10.5%) experienced a CR, 10 (52.6%) achieved a PR, and 7 (36.8%) had SD with a range of 1% to 17% tumor shrinkage.

Treatment was discontinued for grade 1–4 irAEs and most patients experienced grade 2 (n = 9, 47.8%) or grade 3 (n = 10, 52.6%) toxicities. Ongoing irAEs were limited in patients who had a TTP from the date of treatment cessation of < 6 months (n = 1); however, those (n = 6/13) who had a TTP from the date of treatment cessation of ≥6 months had ongoing toxicities related to anti–PD-1/PD-L1 treatment at the time of this analysis.

The median TTP from the date of treatment cessation for this cohort was 18.4 months (95% CI, 4.7–54.3) per Kaplan–Meier estimate (Fig. 1). More than two thirds of the patients (n = 13,

Table 3. Immune-related toxicities and their treatments

ID	Toxicities	Steroids treatment	Duration of steroids treatment	Ongoing toxicities
1	Grade 4 amylase and lipase elevation	No	N/A	No
2	Grade 3 pneumonitis	Yes	2.0	No
3	Grade 2 pericarditis	No[a]	N/A	No
4	Grade 4 myositis, grade 3 myocarditis	Yes[b]	2.0	No
5	Grade 3 hepatitis	Yes	4.8	No
6	Grade 2 arthropathy, grade 2 rash	Yes	12.7[c]	Yes
7	Grade 2 pneumonitis	Yes	2.3	Yes
8	Grade 2 blepharitis	Yes	1.7	No
9	Grade 3 hypothyroidism	Yes	1.6	Yes
10	Grade 3 polyarthralgias and grade 3 diabetes	Yes	0.5	Yes
11	Grade 4 lipase/amylase elevation; grade 2 arthralgia; grade 3 diarrhea	Yes[b]	15.0[+]	Yes
12	Grade 1 iritis, grade 2 arthralgias, grade 1 diarrhea	Yes	1.2	No
13	Grade 3 hypophysitis	Yes	17.4[c]	Yes
14	Grade 1 sinusitis, grade 2 pruritus	No[d]	N/A	No
15	Grade 3 acute interstitial nephritis	Yes	1.4	No
16	Grade 3 joint pain	Yes[b]	14.8[c]	Yes
17	Grade 2 myositis	Yes	29.1[c]	Yes
18	Grade 2 uveitis, grade 3 Jaccoud's arthropathy	Yes	48.1[c]	Yes
19	Grade 1 pneumonitis/diffuse pulmonary infiltrates	Yes	2.4	No
	Total, *n*	16	N/A	9

N/A, not applicable.
[a]Treated with colchicine.
[b]Patients were additionally treated with immunomodulators: intravenous immunoglobulin and infliximab (ID4). Choloroquine and methotrexate (ID11), and methotrexate (ID 16).
[c]Steroid use is ongoing.
[d]Treated with diphenhydramine.

68.4%) had a TTP from the date of treatment cessation of >6 months and 36.8% ($n = 7$) remained progression free for over a year (Table 4). Nearly half ($n = 9$, 47.8%) of the patients have ongoing clinical benefit after discontinuing anti–PD-1/PD-L1 (Fig. 2).

Six patients (31.6%) progressed within 6 months of their last dose of the PD-1/PD-L1 inhibitor and were treated with subsequent systemic therapy. These patients were all on treatment with anti–PD-1/PD-L1 for <6 months. All six patients received subsequent therapy with VEGF inhibitors. Most of these patients ($n = 4$) were treated with cabozantanib, a TKI against VEGFR-2, c-MET, and AXL; 2 of the 4 (50%) patients had a subsequent PR. Four patients (21.1%) progressed ≥6 months after anti–PD-1/PD-L1 discontinuation. Three of these patients developed tumor growth in isolated areas treated with surgical intervention only. These three patients remain off any subsequent systemic therapy since the time of surgical resection. The fourth patient experienced disease progression about 18 months after the last dose of anti–PD-1/PD-L1 and was started on pazopanib, a VEGF TKI, whose best response was stable disease.

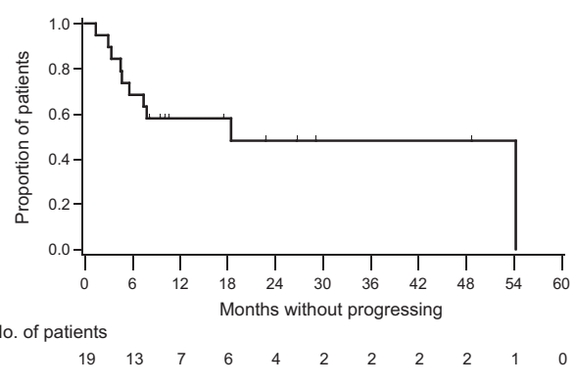

Figure 1.
Kaplan–Meier plot of TTP from the date of treatment cessation.

Discussion

Blockade of the PD-1 pathway confers an adaptive memory immune response that resets the equilibrium between the tumor and the host immune response (19, 20). Hence, it has the potential to provide an ongoing antitumor response even after treatment cessation, which can also translate to ongoing immune-related toxicities. Despite this premise, the current practice is to administer PD-1/PD-L1 inhibitors on a continuous basis until disease progression or development of toxicities, even if a patient is in complete remission. In this report, we sought to examine the outcomes of mRCC patients who had benefitted from PD-1/PD-L1 inhibitors, then had to discontinue treatment after development of irAEs. We observed that a subset of patients (68.4%, $n = 13$) maintain clinical benefit for at least 6 months after treatment discontinuation from PD-1/PD-L1 inhibitors. Although our sample size is limited, this is the first comprehensive analysis in mRCC of outcomes following discontinuation of PD-1/PD-L1 treatment.

Persistent durable responses after treatment discontinuation have been reported with immune-based therapies, such as ipilimumab, nivolumab, and IL2 (24–28). In mRCC, a subset of patients (80%, $n = 4$) who discontinued nivolumab treatment for reasons other than disease progression have maintained their response for 19 to 59 weeks off therapy (26). In melanoma patients treated with ipilimumab and nivolumab, 90% (28 out of 31) of patients who discontinued treatment due to toxicities had persistent responses for more than 6 months off therapy (7), including 68% (21 out of 31) with ongoing responses at the time of the reported analysis. PD-1/PD-L1 blockade rescues "exhausted" T cells, leading to the activation of T-cell effector

Table 4. Summary of patient outcomes in those patients who achieved a clinical response/benefit to PD-1/PD-L1 blockade

ORR to PD-1/PD-L1, *N* (%)	Time on therapy, median (range; months)	TTP from the date of treatment cessation, months (CI)[a]	Ongoing TTP from the date of treatment cessation, *N* (%)	TTP from the date of treatment cessation $\geq$ 6 months, *N* (%)
12 (63.2%)	5.5 (0.7–46.5)	18.4 (4.7–54.3)	9 (47.4%)	13 (68.4%)

ORR, objective response rate by RECIST (rest had SD with tumor shrinkage).
[a]Per Kaplan–Meier estimation.

function and transition to memory cells (19). These drugs have prolonged half-lives, and experiments suggest that PD-1 receptor occupancy does not increase when multiple doses are given within less than 2 months, arguing against the need for continuous treatment with PD-1/PD-L1 inhibitors (29).

Approximately a third of the patients in our analysis ($n = 6$) progressed within 6 months of treatment cessation, demonstrating a need for clinical or molecular biomarkers that can predict the durability of response. Although several clinical factors have been found to be associated with outcomes of PD-1/PD-L1 immunotherapy, none have been studied in the setting of treatment cessation. For example, melanoma patients who develop irAEs (particularly $\geq$ 3 irAEs) and those who received steroids have more favorable outcomes to nivolumab (5, 21). Similar associations have been proposed with CTLA-4 blockade (ipilimumab) in melanoma patients (28, 30, 31). Prospective studies with larger patient cohorts are warranted to examine the predictors of response and survival in patients who discontinue PD-1/PD-L1 immunotherapy in mRCC.

Immune-related end-organ damage in patients treated with immune checkpoint inhibitors is not well understood. A study of lung cancer patients ($n = 482$) investigating the safety and efficacy of anti–PD-1/PD-L1 retreatment after irAEs found that 23% of patients developed a new irAE after restarting therapy, 26% had recurrence of the original irAE, and 51% did not experience a subsequent irAE. Only 8% of patients who were retreated with anti–PD-1/PD-L1 experienced an objective response (32). An autopsy study of a patient who received sequential immune checkpoint blockers and died of metastatic disease showed histologically significant inflammation involving multiple organs, even though this patient only exhibited clinical symptoms of pneumonitis. This patient had subclinical inflammation of the heart, central nervous system, liver, and bone marrow at the time of death (33).

In our cohort, response to treatment has been defined according to RECIST criteria v.1.1. However, some patients treated with immune checkpoint inhibitors experience pseudoprogression, which may be mislabeled as progression according to the RECIST criteria (24, 26, 27). Radiographic progression could be due to scarring and infiltration by tumor immune cells, rather than tumor growth and disease progression (24, 26, 27). As such, immune-related response criteria have been developed to more appropriately categorize response in patients receiving immune-based therapies. Hence, responses to PD-1/PD-L1 blockade and their duration may be underestimated, including the ones reported in our analysis.

Our study and previous reports show that some patients maintain the benefit of PD-1/PD-L1 blockade even after treatment discontinuation (24, 26, 27). The need for continuous dosing of PD-1/PD-L1 inhibitors should be investigated in prospective

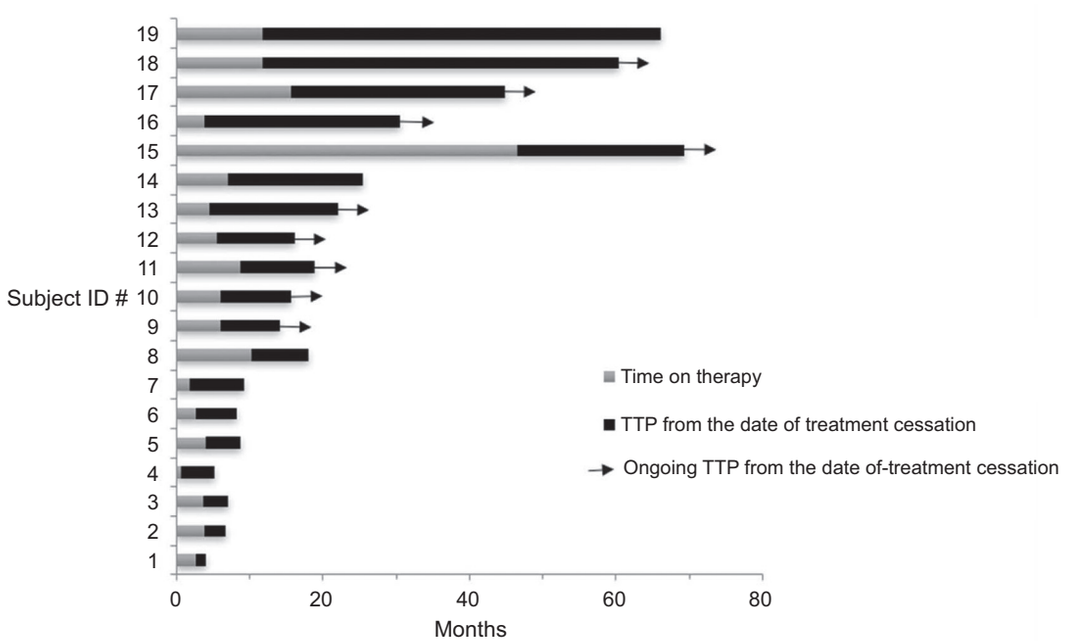

Figure 2.
Swimmer plot representation of patient outcomes.

clinical trials due to the memory component of the immune response and the long effect of PD-1/PD-L1 blockade on the tumor. In mRCC, the impact of nivolumab discontinuation in patients who cease treatment after a confirmed response will be investigated in a phase II study of Optimized Management of NIVOlumab based on REsponse in patients with advanced RCC (OMNIVORE). Other studies are also exploring a customized approach to PD-1/PD-L1 treatment in mRCC (NCT02917772; ref. 34).

Although our study comprehensively reports on patient outcomes after discontinuation of PD-1/PD-L1 inhibitors in mRCC, it carries some limitations. Despite the multicenter nature of the study, our sample size is limited, treatments received were somewhat heterogeneous, imaging was performed at various time points, and the range of follow-up time varied widely. This is also a retrospective analysis and, therefore, is subject to selection bias.

In conclusion, our analysis shows that a subset of mRCC patients treated with PD-1/PD-L1 inhibitors who must discontinue treatment due to irAEs experienced a durable clinical benefit after therapy was halted. These data are hypothesis generating, and larger studies that investigate the tumor and immune microenvironment are warranted to evaluate the long-term outcomes, as well as to identify predictors of response and survival in these patients. Our data confirm the appropriateness of prospective clinical trials designed to assess the need for continuous drug dosing with these agents.

Disclosure of Potential Conflicts of Interest

R.R. McKay reports receiving a commercial research grant from Pfizer and Bayer L.C. Harshman reports receiving commercial research grants from Bayer, Sotio, BMS, Merck, Takeda, Dendreon/Valient, Janssen, Medivation/Astellas, Pfizer, and Genentech, is a consultant/advisory board member for Merck, Exelixis, Pfizer, Corvus, Bayer, Astellas, Kew Group, and Theragene, and has received an expert testimony from CME course: Physican Education Resource and CME course: Applied Clinical Education. F. Schutz has received honoraria from speakers bureau of BMS and Merck, is consultant/advisory board member for Roche, Merck, and BMS. B. McGregor is a consultant/advisory board member for Genentech, Astellas-Seattle Genetics, Exelixis, Nektaar, AstraZeneca, Bayer, Astellas, and Clinical Care Options. G. de Velasco is a consultant/advisory board member for BMS. T.K. Choueiri reports receiving other commercial research support from Pfizer, Exelixis, BMS, and Novartis, is a consultant/advisory board member for Pfizer, Exelixis, Novartis, Ipsen, BMS, Merck, Genentech, and Bayer. No potential conflicts of interest were disclosed by the other authors.

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