Title

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Journal

Journal of Clinical Oncology, 38(27)

ISSN

0732-183X

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Publication Date

2020-09-20

DOI

10.1200/jco.19.03315

Peer reviewed

rapid communications

Salvage Ipilimumab and Nivolumab in Patients With Metastatic Renal Cell Carcinoma After Prior Immune Checkpoint Inhibitors

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abstract

PURPOSE Immune checkpoint inhibitors (ICIs) are standard therapy in metastatic renal cell carcinoma (RCC). The safety and activity of the combination of ipilimumab and nivolumab in patients who have received prior ICI targeting the programmed death 1 (PD-1) pathway remains unknown. We evaluated ipilimumab and nivolumab in patients with metastatic RCC after prior treatment with anti–PD-1 pathway–targeted therapy.

PATIENTS AND METHODS Patients with metastatic RCC who received prior anti–PD-1 pathway-targeted therapy and subsequently received ipilimumab and nivolumab were reviewed. Objective response rate and progression-free survival per investigator assessment were recorded. Toxicity of ipilimumab and nivolumab was also assessed.

RESULTS Forty-five patients with metastatic RCC were included. All patients (100%) received prior ICIs targeting the PD-1 pathway. The median age was 62 years (range, 21-82 years). At a median follow-up of 12 months, the objective response rate to ipilimumab and nivolumab was 20%. The median progression-free survival while on ipilimumab and nivolumab was 4 months (range, 0.8-19 months). Immune-related adverse events (irAEs) of any grade with ipilimumab and nivolumab were recorded in 29 (64%) of the 45 patients; grade 3 irAEs were recorded in 6 (13%) of the 45 patients.

CONCLUSION Ipilimumab and nivolumab demonstrated antitumor activity with acceptable toxicity in patients with metastatic RCC who had prior treatment with checkpoint inhibition.

J Clin Oncol 38:3088-3094.

INTRODUCTION

Renal cell carcinoma (RCC) is an immune-responsive tumor, with immune-modulating agents as a component of standard systemic therapy. Before approval of vascular endothelial growth factor (VEGF) pathway inhibitors, cytokines, including interferon (IFN) and interleukin-2 (IL-2), were standard of care in patients with metastatic RCC, despite modest efficacy and significant toxicities.[1,2] An improved understanding of immune response and the tumor microenvironment has led to the resurgence of immunotherapy in RCC.[3] The recent development of immune checkpoint inhibitors (ICIs) targeting the programmed death 1 (PD-1) and cytotoxic T-cell lymphocyte antigen-4 (CTLA-4) pathways has led to significant advances in the treatment of metastatic RCC.[3]

Nivolumab, an anti–PD-1 antibody, was initially approved as monotherapy after failure of prior VEGF pathway–directed therapy.[4] More recently, the combination of nivolumab and ipilimumab, an anti–CTLA-4 antibody, was approved in the first-line setting for patients with International Metastatic Database Consortium (IMDC) intermediate- and poor-risk disease on the basis of objective response rate (ORR) and overall survival advantages compared with sunitinib.[5] Furthermore, pembrolizumab, an anti–PD-1 antibody, as well as avelumab, an anti–programmed death-ligand 1 (PD-L1) antibody, each in combination with axitinib, a VEGF receptor inhibitor, were approved for the frontline treatment of metastatic RCC.[6,7] Thus, ICI-based therapy is now standard initial therapy in patients with metastatic RCC. Despite these advances, most patients with metastatic RCC will progress. Upon progression, options include agents directed against the VEGF or mammalian target of rapamycin pathways. The benefit of subsequent checkpoint inhibition with ipilimumab and nivolumab in patients who had prior exposure to anti–PD-1 or anti–PD-L1 antibody and no prior

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on April 13, 2020 and published at ascopubs.org/journal/jco on June 3, 2020: DOI https://doi.org/10.1200/JCO.19.03315

CONTEXT

Key Objective

Immune checkpoint inhibitors are standard initial treatment in metastatic renal cell carcinoma (RCC). The clinical efficacy of subsequent checkpoint inhibitors in patients with RCC with prior exposure to programmed death 1/programmed death-ligand 1 (PD-1/PD-L1) inhibitors is unknown. This analysis reports the clinical outcome of patients with metastatic RCC who had prior treatment with PD-1/PD-L1 inhibitors and subsequently were treated with combination ipilimumab and nivolumab.

Knowledge Generated

Ipilimumab and nivolumab combination demonstrated objective responses in a subset of patients with metastatic RCC who had prior exposure to PD-1/PD-L1 inhibitors.

Relevance

Ipilimumab and nivolumab may be an effective salvage treatment option for select patients with metastatic RCC with prior treatment with PD-1/PD-L1 inhibitors. Additional investigation into this approach to define durability of response and benefit/risk is needed.

exposure to an anti–CTLA-4 antibody is not well defined in RCC. A retrospective analysis of patients with metastatic RCC who received prior ICI that targeted the PD-1 pathway and no prior treatment with an anti–CTLA-4 antibody who were treated with salvage ipilimumab and nivolumab was conducted.

PATIENTS AND METHODS

Key eligibility criteria included metastatic RCC of any histology, age ≥ 18 years, at least 1 dose of prior ICI targeting the PD-1 pathway, and treatment with at least 1 subsequent dose of ipilimumab and nivolumab. Medical records were reviewed for the following characteristics: age, sex, histology, prior treatments, best response to prior ICI (defined as best response on any previous line of ICI therapy), median time on prior ICI (defined as the median of the cumulative time of all lines of ICI from the start of therapy until disease progression, discontinued because of unacceptable toxicity, or treatment change), and toxicities to prior ICI. Eastern Cooperative Oncology Group performance status, IMDC risk group, and sites of metastasis at the time of initiation of ipilimumab and nivolumab were also collected.

Study Design and Methods

The primary objective of this study was to estimate an ORR to salvage ipilimumab and nivolumab in patients with metastatic RCC who received ICI as prior treatment. The ORR was defined as the percentage of patients having a confirmed investigator-assessed best response of complete response or partial response (PR) according to RECIST version 1.1.[8] Best objective response (BOR) was defined as the best response designation recorded compared with baseline between the first dose of ipilimumab and nivolumab and the date of documented progression per RECIST version 1.1 or last recorded follow-up. Secondary objectives of interest were progression-free survival (PFS), duration of response (DOR), duration of follow-up, and toxicities to ipilimumab and nivolumab. PFS was calculated from the date of ipilimumab and nivolumab initiation to investigator-assessed clinical or radiographic progression by RECIST version 1.1 or death as a result of any cause (whichever occurred first). Patients who were alive with no disease progression were censored at the date of the last visit. DOR was calculated for all treated patients who achieved a complete response or PR and defined as the time between dates of first response and disease progression or death, whichever occurred first. The patients who did not have disease progression or death at the time of data cutoff were censored at the time of last follow-up. Duration of follow-up was defined as the time from the date of first ipilimumab and nivolumab dose to the date of the last follow-up or documented date of death. Safety was assessed throughout the treatment with ipilimumab and nivolumab, and the severity of adverse events (AEs) was evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). AEs that led to ipilimumab and nivolumab discontinuation, treatment delays, specific intervention treatment, and need for corticosteroids were collected. Numerical variables were summarized with median and range; categorical variables were summarized with frequencies and percentages.

RESULTS

Baseline Characteristics

Forty-five patients with metastatic RCC from 5 medical centers in the United States who received prior ICI targeting the PD-1 pathway and who received at least one dose of salvage ipilimumab and nivolumab were included. The median age at the time of initiation of ipilimumab and nivolumab was 62 years (range, 21-82 years; Table 1). All patients had more than one metastatic site, and 38% had

TABLE 1. Patient Characteristics at the Time of Initiation of Salvage Ipilimumab and Nivolumab

Variable	No. (%)
Median age at diagnosis, years (range)	62 (21-82)
Sex	
Male	35 (78)
Female	10 (22)
ECOG PS	
0	15 (33)
1	24 (53)
2	3 (7)
Unknown	3 (7)
Histology	
Clear cell	40 (89)
Poorly differentiated	1 (2)
NOS	2 (5)
Sarcomatoid	1 (2)
Tissue not available	1 (2)
Nephrectomy	
Yes	40 (89)
No	5 (11)
IMDC risk group	
Favorable	9 (20)
Intermediate	29 (64)
Poor	3 (7)
Unknown	4 (9)
Site of metastases	
Lung	38 (84)
Mediastinal lymph nodes	19 (42)
Adrenal gland	11 (24)
Bone	18 (40)
Liver	13 (29)
Pancreas	10 (22)
Contralateral kidney	12 (27)
Brain	17 (38)
No. of prior lines of systemic therapy	
1	9 (20)
2	12 (27)
3	8 (18)
4	6 (13)
> 4	10 (22)
Prior VEGF receptor inhibitor[a]	27 (60)
Prior immunotherapy	
Anti–PD-1[b]	34 (76)
Anti–PD-L1[b]	11 (24)
IL-2[c]	14 (31)
Best response to prior ICI	
PR	24 (53)
SD	12 (27)
PD	9 (20)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor; IL-2, interleukin-2; IMDC, International Metastatic Database Consortium; NOS, not otherwise specified; PD, progressive disease; PD-1, programmed death 1; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease; VEGF, vascular endothelial growth factor.

[a]VEGF receptor inhibitor as monotherapy or in combination with an ICI at any point before ipilimumab and nivolumab.

[b]Twenty-nine percent of the total number of patients received > 1 line of prior anti–PD-1 or anti–PD-L1 antibody.

[c]IL-2 alone or in combination with another agent at any point before ipilimumab and nivolumab.

brain metastasis. Twenty percent of the patients were favorable risk on the basis of IMDC criteria, 64% were intermediate risk, 7% were poor risk, and 9% were unknown risk because of missing data.

The median number of prior lines of therapy was 3 (range, 1-7 lines; Appendix Table A1, online only). All patients (100%) received at least one prior therapy targeting the PD-1 pathway; of these, 76% received an anti–PD-1 antibody, and 24% received an anti–PDL-1 antibody before ipilimumab and nivolumab. Of the 45 patients, 27 (60%) received monotherapy with prior anti–PD-1 or anti–PDL-1 antibody, 8 (18%) received an ICI that targeted the PD-1 pathway in combination with a VEGF receptor inhibitor (axitinib, sunitinib, or cabozantinib), 4 (9%) received an ICI in combination with bevacizumab, and 6 (13%) received an ICI in combination with another agent (oral hypoxia-inducible factor 2α inhibitor, CD122 agonist, IFN, anti-CD27 antibody, oral adenosine inhibitor, or combination of bevacizumab and IFN). The median number of prior ICI therapies targeting the PD-1 pathway was 1, with 32 (71%) of the 45 patients receiving one line of prior ICI therapy and 13 (29%) of the 45 patients having received more than one prior ICI regimen (Appendix Table A2). The BOR to prior ICI was PR in 53%, stable disease (SD) in 27%, and progressive disease (PD) in 20% (Table 1). The median time on prior ICIs was 13 months (range, 1-75 months). Immune-related AEs (irAEs) of any grade on prior ICIs were recorded in 15 (33%) of the 45 patients. The most common irAEs of any grade were arthralgia (9%), hepatotoxicity (7%), and diarrhea (4%). Grade 3 irAEs, including hyponatremia, hepatotoxicity, and thrombocytopenia, were recorded in 3 (7%) of the 45 patients.

TABLE 2. BOR to Prior ICI and to Salvage Ipilimumab and Nivolumab

BOR to Prior ICI	No. (%)	BOR to Salvage Ipilimumab and Nivolumab	No. (%)
PR	24 (53)	PR	4 (17)
		SD	2 (8)
		PD	17 (71)
		NE	1 (4)
SD	12 (27)	PR	3 (25)
		SD	5 (42)
		PD	4 (33)
PD	9 (20)	PR	2 (22)
		PD	7 (78)

Abbreviations: BOR, best objective response; ICI, immune checkpoint inhibitor; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Clinical Outcome to Ipilimumab and Nivolumab

A total of 45 patients were considered evaluable for treatment response to salvage ipilimumab and nivolumab. The median duration of follow-up was 12 months (range, 0.8-21 months). The ORR to ipilimumab and nivolumab was 20%; 9 patients (20%) had PR, 7 (16%) had SD, and 28 (62%) had PD. One patient (2%) was lost to follow-up after receiving 4 cycles of induction ipilimumab and nivolumab and, therefore, was not evaluable (NE). The median PFS was 4 months (range, 0.8-19 months), and the median DOR was 7 months (range, 2-17 months). Among the 9 patients who had PR, 6 (67%) had an ongoing response, and 5 (55%) were receiving maintenance nivolumab at the time of data analysis. The best response to salvage ipilimumab and nivolumab according to best response to prior ICI is listed in Table 2.

Twenty-three patients received monotherapy with ICI immediately before ipilimumab and nivolumab; of these, 3 (13%) had PR, 13 (57%) had PD, 6 (26%) had SD, and 1 (4%) was NE as best response to ipilimumab and nivolumab. All 5 patients (100%) who received ICI in combination with VEGF receptor inhibitor immediately before ipilimumab and nivolumab had PD as best response to ipilimumab and nivolumab. Of the 6 patients who received monotherapy with VEGF receptor inhibitor immediately before ipilimumab and nivolumab, 5 (83%) had PD, and 1 (17%) had PR as best response to salvage ipilimumab and nivolumab. The clinical characteristics of the patients who had a PR to salvage ipilimumab and nivolumab are listed in Table 3.

The median time between the last dose of prior ICI and initiation of salvage ipilimumab and nivolumab was 2.8 months (range, 0.7-21 months) in patients who had a PR, 5 months (range, 0.4-64 months) in those who had PD as best response, and 0.7 months (range, 0.5-13 months) who had SD as best response to salvage ipilimumab and nivolumab. Of the 31 patients who were IL-2 naïve before ipilimumab and nivolumab, the BOR to ipilimumab and nivolumab was PR in 7 (23%), SD in 5 (16%), PD in 18 (58%), and 1 patient (3%)

TABLE 3. Characteristic of Patients With a Partial Response to Ipilimumab and Nivolumab

Patient No.	Age (years)	IMDC Risk Group	Prior Lines of Therapy, Including Prior ICI[a]	Prior ICI[b]	Time on Prior ICI (months)	BOR to Prior ICI	Time on Ipilimumab Plus Nivolumab (months)	Toxicities to Ipilimumab Plus Nivolumab
1	62	Intermediate	Avelumab plus axitinib, cabozantinib	Avelumab plus axitinib	21	SD	12	None
2	59	Intermediate	Placebo plus sorafenib or X^ plus sorafenib, pazopanib, nivolumab plus oral HIF-2α inhibitor	Nivolumab plus oral HIF-2α inhibitor	13	SD	8	None
3	58	Favorable	Axitinib, nivolumab	Nivolumab	12	SD	10	None
4	65	Intermediate	Nivolumab plus CD122 agonist	Nivolumab plus CD122 agonist	10	PR	5	Grade 2 diarrhea
5	74	Intermediate	Nivolumab	Nivolumab	4	PR	11	Grade 1 skin rash
6	49	Intermediate	IL-2, pazopanib, axitinib, atezolizumab plus IFN, lenvatinib plus everolimus, oral HIF-2α inhibitor	Atezolizumab plus IFN	17	PR	4	Grade 1 night sweats
7	46	Intermediate	Atezolizumab plus bevacizumab, IL-2	Atezolizumab plus bevacizumab	32	PR	4	Grade 2 thyroiditis
8	58	Intermediate	IL-2, CD134 agonist, nivolumab, CD122 agonist	Nivolumab	2	PD	12	None
9	82	Intermediate	Nivolumab	Nivolumab	4	PD	4	None

Abbreviations: BOR, best overall response; HIF-2α, hypoxia-inducible factor 2α; ICI, immune checkpoint inhibitor; IFN, interferon; IL-2, interleukin-2; IMDC, International Metastatic Database Consortium; PD, progressive disease; PR, partial response; SD, stable disease; X^, investigational anti-angiopoietin peptibody.

[a]Prior lines of therapy in chronologic order.

[b]Prior ICI at any point before ipilimumab and nivolumab.

was NE. Of the 14 patients who were exposed to IL-2 before ipilimumab and nivolumab, the BOR to ipilimumab and nivolumab was PR in 2 (14%), SD in 2 (14%), and PD in 10 (72%).

Safety of Ipilimumab and Nivolumab

The median time on ipilimumab and nivolumab was 4 months (range, 0.7-19 months). A total of 31 patients (69%) received all 4 doses of induction ipilimumab and nivolumab. The induction phase of ipilimumab and nivolumab was completed in 23 (51%) of the 45 patients without delay or treatment interruption. Treatment was delayed in 4 patients (9%) and discontinued in 6 (13%) because of irAEs. Four patients (9%) had interruption in treatment because of non–treatment-related AEs. One patient developed splenic rupture 1 week after the first cycle of ipilimumab and nivolumab secondary to a splenic artery aneurysm and underwent surgical management of the aneurysm; treatment with ipilimumab and nivolumab was later resumed without issue. One patient underwent stereotactic radiosurgery for metastatic brain lesions after the first cycle of ipilimumab and nivolumab, and treatment with ipilimumab and nivolumab was later resumed. Treatment was delayed in 2 patients because of infection. Treatment with ipilimumab and nivolumab was discontinued in 5 patients (11%) because of PD, and 3 patients (7%) died as a result of PD during the induction phase.

irAEs for ipilimumab and nivolumab of any grade were recorded in 29 (64%) of the 45 patients, with 6 (13%) reporting grade 3-4 irAEs (Table 4). The most common irAEs of any grade were diarrhea (16%), rash (13%), hepatotoxicity (9%), and pneumonitis (7%). The most common grade 3-4 irAEs were hepatotoxicity (7%) and pneumonitis, rash, diarrhea, thrombocytopenia, and colitis (2% each). Because of irAEs, 17 (38%) of the 45 patients received systemic corticosteroids (of any dose), and 9 (20%) received high-dose corticosteroids (defined as ≥ 40 mg of prednisone equivalent daily for 2 weeks). One patient (2%) was treated with infliximab for grade 3 colitis. There were no treatment-related deaths directly attributable to ipilimumab and nivolumab.

TABLE 4. Treatment-Related Immune Adverse Events to Ipilimumab and Nivolumab

	Grade, No. (%)	
Adverse Event	**Any**	**3-4**
Diarrhea[a]	7 (16)	1 (2)
Skin rash[b]	6 (13)	1 (2)
Hepatotoxicity[a,c]	4 (9)	3 (7)
Pneumonitis[b]	3 (7)	1 (2)
Arthralgia	3 (7)	
Fatigue	2 (4)	
Thyroiditis	2 (4)	
Colitis	2 (4)	1 (2)
Dry mouth	1 (2)	
Enteritis	1 (2)	
Polymyalgia like syndrome	1 (2)	
Nephritis	1 (2)	
Thrombocytopenia	1 (2)	1 (2)

NOTE. Treatment-related immune adverse events are listed in descending order of frequency.

[a]One patient developed grade 3 diarrhea and grade 3 hepatotoxicity.

[b]One patient developed grade 3 pneumonitis and grade 3 skin rash.

[c]Hepatotoxicity includes AST and/or ALT elevation.

DISCUSSION

Ipilimumab and nivolumab is now standard initial therapy in IMDC intermediate- and poor-risk metastatic RCC. In addition, pembrolizumab as well as avelumab in combination with axitinib are approved initial options in first-line treatment of metastatic RCC. Despite significant clinical activity, a substantial percentage of patients who receive prior anti–PD-1 pathway–targeted therapy will eventually progress and require further systemic therapy. The role of additional checkpoint inhibition with ipilimumab and nivolumab in patients with prior exposure to anti–PD-1 pathway–targeted therapy but no prior exposure to anti–CTLA-4 pathway–targeted therapy remains undefined.

The current series demonstrates that objective PRs with salvage ipilimumab and nivolumab are possible in a subset of patients with metastatic RCC who are naïve to anti–CTLA-4 antibody and had prior exposure to therapy targeting the PD-1 pathway. Ipilimumab and nivolumab have been evaluated in previously treated patients with metastatic RCC.[9] Approximately one third of the patients enrolled in CheckMate 016 had prior treatment with cytokines, and 19% had prior VEGF receptor inhibitor treatment, but none of the patients had prior exposure to ICIs. The ORR to ipilimumab and nivolumab was 40%, which demonstrates that ipilimumab and nivolumab are effective in patients previously treated with a cytokine or a VEGF receptor inhibitor.

Ipilimumab and nivolumab act in different phases of the immune response. CTLA-4 blockade affects the immune priming phase and induces the proliferation of effector T cells, regardless of T-cell receptor specificity.[10] PD-1 blockade works during the effector phase and restores the immune function of T cells, which are exhausted as a result of high antigen exposure, as in advanced cancers.[11,12] CTLA-4 blockade induces a proliferative gene expression signature predominantly in a subset of transitional memory T cells, whereas PD-1 blockade causes changes in genes involved in cytolysis and natural killer cell function.[13] The differences in timing, site of action, and nonoverlapping changes in genes involved in antitumor response by anti–CTLA-4–targeted antibodies and anti–PD-1 antibodies have the potential of additive or synergistic effects in the

treatment of advanced cancers.[13] Thus, the mechanistic differences between an anti–CTLA-4 antibody and an anti–PD-1 antibody may allow activity of anti–CTLA-4 antibody in combination with anti–PD-1 antibody upon failure of prior anti–PD-1 pathway–targeted therapy.

Salvage ipilimumab and nivolumab therapy after single-agent nivolumab is currently being evaluated in multiple clinical trials. The TITAN trial enrolled patients with treatment-naïve advanced RCC with a clear cell component to upfront nivolumab therapy with the addition of ipilimumab in patients who have PD or SD.[14] This study demonstrated an approximately 10% increase in ORR with the addition of ipilimumab to nivolumab. Two additional prospective trials, HCRN GU16-260 (ClinicalTrials.gov identifier: NCT03117309) and OMNIVORE (ClinicalTrials.gov identifier: NCT03203473) are evaluating the clinical outcome of the addition of ipilimumab in patients with metastatic RCC who do not achieve an objective response to nivolumab monotherapy. However, these studies enroll patients in the first-line setting and exclude patients exposed to prior ICIs. Of note, a subset of patients in this series with lack of an objective response to prior ICI-based therapy achieved a PR to salvage ipilimumab and nivolumab.

The percentage of patients who achieved a PR to salvage ipilimumab and nivolumab was not different on the basis of response to prior ICI regimens, which suggests that susceptibility to a CTLA-4 inhibitor–containing regimen is distinct from factors affecting response to regimens targeting the PD-1 pathway. A related observation was that median time between prior ICI and salvage ipilimumab and nivolumab initiation was shorter in responders to salvage ipilimumab and nivolumab compared with patients with PD, which raises the hypothesis that immediate treatment with a combination of anti–PD-1 pathway–targeted antibody and anti–CTLA-4 antibody may be associated with improved response.

Of note, the majority of patients in this study who received VEGF receptor inhibitor therapy immediately before ipilimumab and nivolumab did not have an objective response to salvage ipilimumab and nivolumab. Although limited by small numbers, this observation raises hypotheses about the immunomodulatory effects of immediate prior VEGF pathway inhibition in this setting.

This analysis has several limitations, including small sample size, the inherent bias in a retrospective analysis, lack of central blinded independent review to assess response to treatment, relatively short follow-up, and incomplete data collection in some patients. Of note, patients in this cohort were not exposed to prior ipilimumab and nivolumab, and few patients had ICI plus VEGF receptor inhibitor combination therapy, which are now the standard initial therapy in metastatic RCC. Thus, the utility of salvage ipilimumab and nivolumab in patients receiving one of these ICI-based combinations is largely unknown. The current data may be more relevant to patients who receive ICI monotherapy either after VEGF pathway targeted therapy in the frontline setting or as is being investigated in the adjuvant setting.

This series demonstrates that patients with metastatic RCC can achieve objective responses to salvage ipilimumab and nivolumab after prior anti–PD-1 pathway–targeted therapy. It is important to note that although a small proportion of patients had an objective response to salvage ipilimumab and nivolumab, the responses to salvage ipilimumab and nivolumab were durable in the majority of responders, and several patients derived clinical benefit even without achieving RECIST-defined PR. However, the lack of complete responses, high rate of PD, and the potential for toxicity provide caution to the application of these data to select patients. Prospective clinical trials are needed to further define the clinical activity of checkpoint inhibition after previous ICI exposure in metastatic RCC.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.03315.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Salvage Ipilimumab and Nivolumab in Patients With Metastatic Renal Cell Carcinoma After Prior Immune Checkpoint Inhibitors

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Travel, Accommodations, Expenses: Pfizer, Bristol-Myers Squibb, Merck

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Prior Systemic Therapies Other Than Prior ICI

Systemic Therapy	No. (%)
Cabozantinib	8 (18)
Axitinib	4 (9)
Pazopanib	5 (11)
Sunitinib	7 (6)
Gemcitabine plus sunitinib	1 (2)
Sorafenib	2 (4)
Axitinib plus TNF inhibitor	1 (2)
Axitinib plus CXCR4 inhibitor	1 (2)
Bevacizumab	1 (2)
ALT immunomodulation	1 (2)
Bevacizumab plus erlotinib	1 (2)
Oral HIF-2α inhibitor	2 (4)
CD134 agonist	2 (4)
CD122 agonist	2 (4)
IL-2	13 (29)
CSF1R inhibitor plus CD40 antibody	1 (2)
Lenvatinib plus everolimus	2 (4)

Abbreviations: CSF1R, colony-stimulating factor 1 receptor; CXCR4, CXC chemokine receptor 4; HIF-2α, hypoxia-inducible factor 2α; ICI, immune check point inhibitor; IFN, interferon; IL-2, interleukin-2; TNF, tumor necrosis factor.

TABLE A2. Prior ICIs

ICI	No. (%)
Nivolumab	28 (62)
Pembrolizumab	2 (4)
Atezolizumab	3 (7)
Nivolumab plus axitinib	1 (2)
Nivolumab plus sunitinib	2 (4)
Nivolumab plus cabozantinib	2 (4)
Avelumab plus axitinib	3 (7)
Pembrolizumab plus axitinib	1 (2)
Pembrolizumab plus CD137 agonist	1 (2)
Pembrolizumab plus pegylated IFN	1 (2)
Atezolizumab plus bevacizumab	4 (9)
Pembrolizumab plus bevacizumab	1 (2)
Nivolumab plus oral HIF-2α inhibitor	1 (2)
Nivolumab plus CSF1R inhibitor plus CD40 agonist	1 (2)
Nivolumab plus CD122 agonist	1 (2)
Nivolumab plus IL-2	1 (2)
Atezolizumab plus IFN	2 (4)
Atezolizumab plus bevacizumab plus IFN	1 (2)
Atezolizumab plus anti-CD27 antibody	1 (2)
Atezolizumab plus oral adenosine inhibitor	1 (2)

NOTE. Twenty-nine percent of the patients received > 1 line of prior anti–PD-1 or anti–PD-L1 antibody.

Abbreviations: CSF1R, colony-stimulating factor 1 receptor; HIF-2α, hypoxia-inducible factor 2α; ICI, immune checkpoint inhibitor; IFN, interferon; IL-2, interleukin-2.