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Original Research

Combination Immune Checkpoint Blockade Regimens for Previously Untreated Metastatic Renal Cell Carcinoma: The Winship Cancer Institute of Emory University Experience

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ABSTRACT

Introduction: There are three combination immune checkpoint inhibitor (ICI)–based regimens in the first-line setting for metastatic renal cell carcinoma (mRCC). Currently, there is limited real-world data for clinical outcomes and toxicity in mRCC patients treated with first-line ICI-based regimens. **Methods:** We performed a retrospective review of 49 mRCC patients treated with ICI-based combination regimens in the standard of care setting at the Winship Cancer Institute of Emory University from 2015–2020. We collected baseline data from the electronic medical record including demographic information and disease characteristics. Immune-related adverse events (irAEs) were collected from clinic notes and laboratory values. The primary clinical outcomes measured were overall survival (OS), progression-free survival (PFS), and objective response rate (ORR). **Results:** The median age was 65 years, and most patients (80%) were males. The majority were White (86%) and had clear cell RCC (83%). Most patients had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 (43%) or 1 (45%). Approximately one-half (49%) had at least three sites of distant metastatic disease. Most patients (88%) received nivolumab and ipilimumab. More than one-half (53%) of patients experienced an irAE, with 13 (27%) patients having treatment delayed and 18% discontinuing treatment for toxicity. The median OS was not reached, and the median PFS was 8.0 months per a Kaplan-Meier estimation. More than half of patients (53%) had a PFS $>$ 6 months, and 22% had PFS $>$ 1 year. The ORR was 33% for the entire cohort, and 7% of patients had a complete response. **Conclusion:** We presented real-world efficacy and toxicity data for front-line ICI combination treatment regimens. The ORR and median PFS were lower in our cohort of patients compared to the available data in the clinical trial setting. This was likely because of more advanced disease in this study. Future studies should provide additional data that will allow comparisons between different ICI combination regimens for untreated mRCC.

Keywords: renal cell carcinoma, immune checkpoint inhibitors, combination therapy, immunotherapy, genitourinary cancer

INTRODUCTION

Immunotherapy has been used as a treatment for metastatic renal cell carcinoma since interleukin-2 (IL-2) was approved in 1992.[1] Immune checkpoint inhibitors (ICIs) began to be investigated in metastatic renal cell carcinoma (mRCC) and nivolumab, a programmed cell death-1 (PD-1) inhibitor, became the first ICI approved for mRCC in 2015.[2] ICIs have a favorable toxicity profile and have promise for durable clinical benefit, albeit for a minority of patients.[3,4] The next advance in immunotherapy for mRCC came in the form of combination regimens, both as dual ICI combination regimens and ICIs in combination with vascular endothelial growth factor (VEGF) inhibitors.[5–9] This has led to the approval of several combination ICI-based regimens in the first-line setting: nivolumab and ipilimumab, nivolumab and cabozantinib, pembrolizumab and axitinib, and avelumab and axitinib.[2] Additionally, pembrolizumab plus lenvatinib is currently listed on the national comprehensive cancer network (NCCN) guidelines as a treatment option for mRCC.[10] Currently, there are no data comparing the efficacy of these first-line ICI-based regimens.

Combination immunotherapy regimens come in two main regimens: dual ICI, which includes nivolumab and the cytotoxic T-cell lymphocyte associated protein 4 (CTLA-4) inhibitor ipilimumab or ICI and VEGF-targeted combination therapy with pembrolizumab or avelumab and axitinib. There are also several ongoing phase 3 clinical trials investigating the efficacy of ICI combination regimens in previously untreated RCC that may lead to additional FDA approvals (ClinicalTrials.gov identifiers: NCT03141177, NCT03937219, NCT03729245, NCT02420821). Furthermore, additional novel combinations of ICI with vaccines, other checkpoints such as TIM-3 or LAG-3, and novel delivery strategies are also in development.[11,12] Hence, understanding the real-world impact of immunotherapy combination regimens is crucially important for medical oncologists who wish to offer contemporary treatment options for their patients with mRCC.

In this study, we present our center's real-world experience with safety and efficacy of ICI-based combination regimens in the first-line setting for the treatment of mRCC. We report clinical outcomes such as response rates, overall survival (OS), and progression-free survival (PFS), as well as immune-related adverse events. Given the increased usage of ICI combinations in the treatment-naïve setting in mRCC, this study has significant clinical utility for medical oncologists in both the academic and community setting.

METHODS

Patients and Data

We performed a retrospective review of 49 patients with mRCC who were treated with ICI-based combination regimens in the standard of care setting at the Winship Cancer Institute of Emory University from 2015–2020. This study was approved by the Winship Cancer Institute of Emory University institutional review board (IRB00100973). Informed consent was not required for this retrospective study. We collected baseline data from the electronic medical record including demographic information, RCC histology, sites of metastatic disease at baseline, class of ICI combination, International Metastatic RCC Database Consortium (IMDC) risk group, body mass index (BMI), platelets, neutrophils, lymphocytes, monocytes, eosinophils, and basophils. Immune-related adverse events (irAEs) were collected from clinic notes and laboratory values throughout the duration of the time on treatment.

Outcomes

The primary clinical outcomes measured were OS, PFS, and objective response rate (ORR). We calculated OS and PFS as the time in months from initiation of ICI combination to date of death or radiographic or clinical progression, respectively. An objective response was defined as a partial response or a complete response (CR) per RECIST v1.1 (Response Evaluation Criteria in Solid Tumours guideline version 1.1).[13] Secondary clinical outcomes were clinical benefit and time to next treatment (TTNT). Clinical benefit was defined as an objective response or stable disease with a PFS $>$ 6 months. TTNT was measured from the initiation of the ICI combination to the initiation of the subsequent line of systemic therapy or date of last follow-up for those patients who had not started a second-line therapy.

Statistical Methods

Summary statistics were used mainly in the analysis, in which continuous variables were summarized as mean, median, minimum (min), maximum (max), and standard deviation, whereas frequency and percentage were reported for categorical variables. Time-to-event outcomes (OS, PFS, and TTNT) were described by the Kaplan-Meier method. SAS 9.4 was used for statistical analysis.

RESULTS

Demographics and Baseline Patient Characteristics

Baseline disease characteristics and demographic information are presented in Table 1. The median age was 65 years, and the majority of patients (79.6%, $n = 39$) were males. Most patients were White (85.7%) with clear cell RCC (83%). Most patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of either 0 ($n = 20$, 43%) or 1 ($n = 21$, 45%). The distribution of metastatic sites at baseline was lymph node ($n = 32$, 65%), bone ($n = 20$, 41%), liver ($n = 40$, 24%), brain ($n = 4$, 8%), and lung ($n = 4$ 0, 82%). Approximately one-half ($n = 24$, 49%) had at least three sites of distant metastatic disease.

Table 1. Demographics and baseline disease characteristics

Variable	Level	*n* (%), *N* = 49
Sex	Male	39 (80)
	Female	10 (20)
Race	White	42 (86)
	Black	7 (14)
ECOG PS	0–1	41 (87)
	2–3	6 (13)
	Missing	2
ccRCC	No	8 (17)
	Yes	39 (83)
	Missing	2
Type of ICI combination	Nivolumab + ipilimumab	43 (88)
	Pembrolizumab + axitinib	6 (12)
Number of distant metastatic sites	1	8 (16)
	2	17 (35)
	3+	24 (49)
Distribution of metastatic sites	Lymph node	32 (65)
	Bone	20 (41)
	Liver	12 (24)
	Brain	4 (8)
	Lung	40 (82)
IMDC risk group	Favorable	9 (18)
	Intermediate	25 (51)
	Poor	15 (31)

ccRCC: clear cell renal cell carcinoma; ECOG PS: Eastern Cooperative Oncology Group performance status; ICI: immune checkpoint inhibitor; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium.

Treatment and Toxicity Data

The breakdown for treatment regimens was 43 nivolumab + ipilimumab and six pembrolizumab + axitinib. The mean time on treatment was 7.2 months (range, 0–31.5 months), with 8% of patients receiving only one dose and 16% of patients receiving treatment for at least 1 year. At the time of this analysis, 35% of patients were still on treatment. More than one-half (n = 26, 53%) of patients experienced an irAE, with 13 (27%) of those patients having their treatment delayed and nine patients (18%) discontinuing treatment for toxicity. Severe irAEs (grade 3 or grade 4 per Common Terminology Criteria for Adverse Events [CTCAE] version 5.0) were experienced by seven patients (14.3%). The most common irAEs were endocrinopathies (n = 13), gastrointestinal irAEs (n = 9), and dermatologic irAEs (n = 8).

Clinical Outcomes

The median OS was not reached, and the median PFS was 8.0 months per Kaplan-Meier estimation (Figs. 1 and 2). Details regarding clinical outcomes are presented in Table 2. The median OS per Kaplan-Meier estimation was not reached at the time of the analysis, whereas the 12-month OS rate was 78.8% and the 36-month OS rate was 58.3%. The median PFS was 8.0 months per the Kaplan-Meier method. The 12-month PFS rate was 37.2%, and the 24-month PFS rate was 27.9%. The ORR was 33% for the entire cohort, and 7% of patients had a CR. All patients who had a best response of CR received

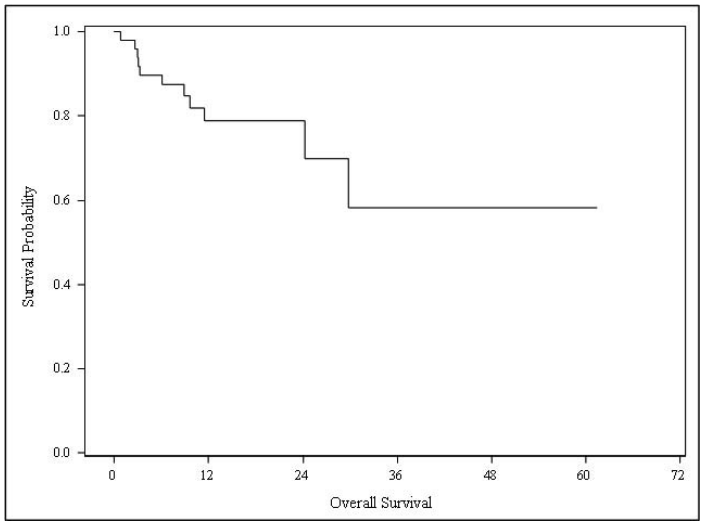

Figure 1. Kaplan-Meier curve for overall survival (OS).

treatment with nivolumab + ipilimumab. Most patients (54%) experienced CB from ICI combination therapy. The median TTNT was 23.6 months; the 12-month and 24-month TTNT survival rates were 61.3% and 46.0%, respectively (Fig. 3). Notably, 24.5% of patients had a TTNT of at least 36 months. Of the eight patients with non-clear cell RCC, three patients (37.5%) had an objective response and five experienced CB (62.5%). The ORR and CB rates for patients with a sarcomatoid component to their RCC histology were 44.4% and 66.7%, respectively. Four patients with a sarcomatoid component remained progression-free for at least 12 months on treatment.

Post-ICI Systemic Therapy Data

Of the 49 patients included in this study, 24 patients (49.0%) did not receive any subsequent therapy. Among the patients who received subsequent lines of systemic

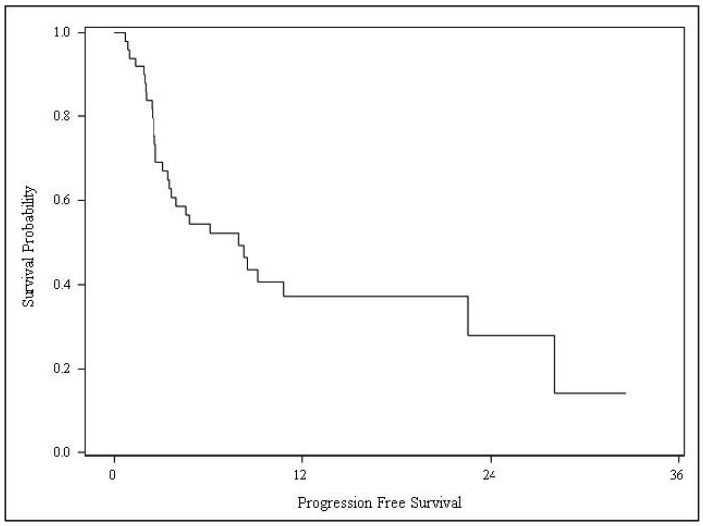

Figure 2. Kaplan-Meier curve for progression-free survival.

Table 2. Summary of clinical outcomes in our cohort

Outcome Variable	Survival Rate, % (95% CI)
OS, median: Not reached	
12 month	78.8 (62.7–88.5)
24 month	78.8 (62.7–88.5)
36 month	58.3 (28.5–79.3)
PFS, median: 8.0 months	
12 month	37.2 (22.6–51.9)
24 month	27.9 (11.1–47.7)
Radiographic responses per RECIST 1.1; ORR = 32.6%, *n* (%)	
Complete response	3 (7)
Partial response	12 (26)
Stable disease	15 (33)
Progressive disease	16 (35)
Nonevaluable	3*
TTNT, median: 23.6 months, % (95% CI)	
12 month TTNT:	61.3 (44.5–74.5)
24 month TTNT:	46.0 (25.7–64.1)
36 month TTNT:	24.5 (5.6–50.4)

*Nonevaluable disease was not included in the overall percentage.
ORR: objective response rate; OS: overall survival; PFS: progression-free survival; RECIST 1.1: Response Evaluation Criteria in Solid Tumours guideline version 1.1; TTNT: time to next treatment.

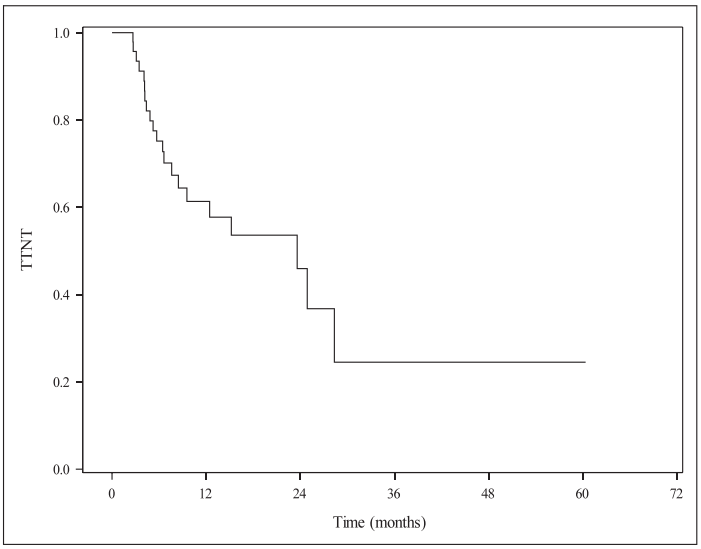

Figure 3. Kaplan-Meier curve for time-to-next treatment (TTNT).

therapy, six patients (12.2%) received immunotherapy-based regimen, one patient received chemotherapy, and the remaining 18 patients (36.7%) received VEGF-targeted therapy, with the most common agent being cabozantinib ($n = 10$, 20.4%).

DISCUSSION

In this study, we are presenting real-world experiences using standard of care immune checkpoint blockade combination treatment regimens in the first-line setting for mRCC. We present survival data, response rates, and toxicity data from patients treated in the standard of care setting outside of clinical trials. These data may be useful for practicing medical oncologists in both the academic and community setting. These data supplements previously published data from the clinical trials investigating immunotherapy combination regimens in the first-line setting.[5,6]

Currently, there are four approved combination immunotherapy regimens in the treatment-naïve setting for mRCC: nivolumab + ipilimumab, nivolumab + cabozantinib, pembrolizumab + axitinib, and avelumab + axitinib. Additionally, pembrolizumab plus lenvatinib is currently on the NCCN guidelines for the treatment of mRCC. Dual ICI treatment with nivolumab and ipilimumab has been shown to be efficacious in several tumor types and offers higher response rates than either agent as monotherapy.[14–16] The rationale for combination ICI treatment is that the PD-1 inhibitor allows the immune system to recognize and attack malignant cells whereas the CTLA-4 inhibitor stimulates the growth and activity of T cells.[17] Combination treatment of ICI and VEGF inhibitors has also shown efficacy for the treatment of mRCC, which may be explained by VEGF inhibition promoting intratumoral T-cell infiltration.[18,19] Although these combination regimens have improved efficacy, medical oncologists must balance the additional antitumor potency of combination regimens with the increased rates of toxicity.

A summary of the landmark phase 3 clinical trials investigating immunotherapy combinations in the first-line setting for mRCC is presented in Table 3. The ORR ranged from 37–71%, with the pembrolizumab + lenvatinib combination having the highest ORR.[8] The pembrolizumab + lenvatinib combination also had the highest CR rate at 16.1%, and the nivolumab + ipilimumab combination had the highest rate of treatment discontinuation for toxicity at 22%. Our cohort of patients comprised nivolumab + ipilimumab and pembrolizumab + axitinib patients. The ORR in our cohort was 33%, which was lower than those for both of the landmark phase 3 trials. This result might be explained in part because there was a higher proportion of IMDC poor-risk patients in our cohort (31%) and nearly half of our patients had three or more distant metastatic sites at baseline. Furthermore, 13% of the patients in this study had an ECOG PS ≥ 2, which was an exclusion criterion for all trials included in Table 3. Our CR rate for nivolumab + ipilimumab patients was similar to the CheckMate 9 ER trial (7% vs 9%). The rate of discontinuation for irAE was also similar in our cohort (18% vs 22%). In short, our real-world results had similar rates of CR and treatment discontinuation from irAE but lower ORR.

Ongoing phase 3 clinical trials with ICI combination regimens include an anti-PD-1 + anti-CTLA-4 + anti-VEGF combination (COSMIC-313) and an anti-PD-1 + pegylated interleukin-2 combination (PIVOT-09). Although combination ICI therapy is approved in the treatment-naïve setting for mRCC, there is an ongoing clinical trial investigating the use of ICI monotherapy followed by dual ICI salvage therapy with nivolumab and ipilimumab

Table 3. Summary of landmark phase 3 trials of immunotherapy combination regimens

Clinical Trial (Identifier)	Investigational Arm	ORR, % (CR %)	IMDC, %	Median PFS, months	irAEs and Grade (d/c rate, %*)
CheckMate-9ER[9] (NCT03141177)	Nivolumab + cabozantinib	55.7 (8.0)	Fav: 22.9 Int: 58.2 Poor: 18.9	16.6	99.7% AE, 75.3% Grade 3+ (5.6)
CLEAR[8] (NCT02811861)	Pembrolizumab + lenvatinib	71.0 (16.1)	Fav: 31.0 Int: 59.2 Poor: 9.3	23.9	99.7% AE, 82.4% Grade 3+ (13.4)
JAVELIN[7] (NCT02684006)	Avelumab + axitinib	51.4 (3.4)	Fav: 21.3 Int: 61.3 Poor: 16.3	13.8	99.5% AE, 38.2% irAE, 71.2% Grade 3+ (7.6)
KEYNOTE-426[6] (NCT02853331)	Pembrolizumab + axitinib	59.3 (5.8)	Fav: 31.2 Int: 56.2 Poor: 12.5	15.1	98.4% AE, 75.8% Grade 3+ (10.7)
CheckMate-214[5] (NCT02231749)	Nivolumab + ipilimumab	42 (9)	Fav: 23 Int: 61 Poor: 21	11.6	93% AE, 46% Grade 3+ (22)
IMmotion151 (NCT02420821)	Atezolizumab + bevacizumab	37 (5)	Fav: 20 Int: 69 Poor: 38	11.2	91% AE, 40% Grade 3+ (5)

*Reported d/c rate is the discontinuation rate of both agents.
AE: adverse events; CR: complete response; d/c: discontinuation; Fav: favorable; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; Int: intermediate; irAE: immune-related adverse events; ORR: objective response rate; PFS: progression-free survival.

(ClinicalTrials.gov identifier: NCT03117309). The results of this trial are pending; however, salvage therapy with nivolumab and ipilimumab in patients who were previously treated with an ICI demonstrated antitumor efficacy with a 20% ORR and a tolerable side effect profile with only 13% of patients experiencing grade 3 or greater irAEs.[20] There have also been promising results for the first-line immunotherapy combination with a dendritic cell–based therapy and sunitinib in intermediate and poor-risk mRCC patients; 62% experienced clinical benefit and a median PFS of 11.2 months in a phase 2 clinical trial.[21] Sequential nivolumab then salvages ICI dual therapy, and novel combination treatment regimens may present safe and efficacious alternatives to the currently approved ICI combination treatments. Future studies comparing clinical outcomes and toxicity between different ICI combination regimens may elucidate the treatment options that are most likely to provide mRCC patients with clinical benefit.

There are limitations in our study that should be addressed. First, we had only six patients treated with pembrolizumab and axitinib, which limited our ability to compare outcomes and toxicity between this regimen and nivolumab + ipilimumab. Additionally, this was a retrospective analysis, which limited our ability to grade all irAEs. Additional data are needed to more accurately compare the differences in clinical outcomes and toxicity between ICI combinations in the standard of care setting.

CONCLUSIONS

In this study, we presented real-world efficacy and toxicity data of ICI combination treatment regimens in treatment-naïve mRCC. The ORR and median PFS were lower in our cohort of patients compared to the response rates from the phase 3 clinical trials that led to the approval of nivolumab + ipilimumab and pembrolizumab + axitinib. This was likely because the patients included in this study had more advanced disease and worse clinical status at the time of treatment initiation compared to patients treated in the clinical trial setting. Future studies should provide additional data, which will allow comparisons between different ICI combination regimens for untreated mRCC.

References

1. Rosenberg SA. Interleukin 2 for patients with renal cancer. *Nat Clin Pract Oncol*. 2007;4:497.
2. FDA Approved Drug Products. Accessed Jun 27, 2020. www.accessdata.fda.gov/scripts/cder/daf
3. McDermott DF, Drake CG, Sznol M, et al. Survival, durable response, and long-term safety in patients with previously treated advanced renal cell carcinoma receiving nivolumab. *J Clin Oncol*. 2015;33:2013–2020.
4. Martini DJ, Hamieh L, McKay RR, et al. Durable clinical benefit in metastatic renal cell carcinoma patients who discontinue PD-1/PD-L1 therapy for immune-related adverse events. *Cancer Immunol Res*. 2018;6:402–408.
5. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med*. 2018;378:1277–1290.
6. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2019;380:1116–1127.
7. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2019;380:1103–1115.
8. Motzer R, Alekseev B, Rha SY, et al. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. *N Engl J Med*. 2021;384:1289–1300.

9. Choueiri TK, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2021;384:829–841.
10. Motzer RJ, Jonasch E, Boyle S, et al. NCCN guidelines insights: kidney cancer, version 1.2021. *J Natl Compr Canc Netw*. 2020;18:1160–1170.
11. Mougel A, Terme M, Tanchot C. Therapeutic cancer vaccine and combinations with antiangiogenic therapies and immune checkpoint blockade. *Front Immunol*. 2019;10:467.
12. Kon E, Benhar I. Immune checkpoint inhibitor combinations: current efforts and important aspects for success. *Drug Resist Updat*. 2019;45:13–29.
13. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228–247.
14. Larkin J, Hodi FS, Wolchok JD. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373:1270–1271.
15. Tomita Y, Kondo T, Kimura G, et al. Nivolumab plus ipilimumab versus sunitinib in previously untreated advanced renal-cell carcinoma: analysis of Japanese patients in CheckMate 214 with extended follow-up. *Jpn J Clin Oncol*. 2020;50:12–19.
16. Hammers HJ, Plimack ER, Infante JR, et al. Safety and efficacy of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma: the CheckMate 016 Study. *J Clin Oncol*. 2017;35:3851–3858.
17. Seidel JA, Otsuka A, Kabashima K. Anti-PD-1 and anti-CTLA-4 therapies in cancer: mechanisms of action, efficacy, and limitations. *Front Oncol*. 2018;8:86.
18. Mollica V, Di Nunno V, Massari F. Pembrolizumab plus axitinib: a new treatment option for patients with metastatic renal cell carcinoma. *Chin Clin Oncol*. 2019;8:S21.
19. Campesato LF, Merghoub T. Antiangiogenic therapy and immune checkpoint blockade go hand in hand. *Ann Transl Med*. 2017;5:497.
20. Gul A, Stewart TF, Mantia CM, et al. Salvage ipilimumab and nivolumab in patients with metastatic renal cell carcinoma after prior immune checkpoint inhibitors. *J Clin Oncol*. 2020;38:JCO1903315.
21. Amin A, Dudek AZ, Logan TF, et al. Survival with AGS-003, an autologous dendritic cell-based immunotherapy, in combination with sunitinib in unfavorable risk patients with advanced renal cell carcinoma (RCC): phase 2 study results. *J Immunother Cancer*. 2015;3:14.