

Phase Ib/II Clinical Trial of Pembrolizumab With Bevacizumab for Metastatic Renal Cell Carcinoma: BTCRC-GU14-003

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PURPOSE We hypothesized that bevacizumab will potentiate activity of pembrolizumab. We conducted a phase Ib/II, single-arm, multisite clinical trial of the combination in metastatic renal cell carcinoma (RCC).

PATIENTS AND METHODS Patients with metastatic clear cell RCC who experienced progression after at least one systemic therapy (phase Ib) or were treatment naïve (phase II) were enrolled. In phase Ib, pembrolizumab (200 mg) and bevacizumab (10 or 15 mg/kg) were given intravenously every 3 weeks. The primary end point for phase II was overall response rate (ORR). With an 80% statistical power and a type I error probability of 0.1, 48 patients were to be accrued to detect an ORR of 42%.

RESULTS Thirteen patients (ages 33-68 years; median, 55 years) were enrolled in the phase Ib study. No dose-limiting toxicities were reported. Pembrolizumab 200 mg and bevacizumab 15 mg/kg were chosen for phase II. Forty-eight patients (ages 42-84 years; median age, 61 years; 33 males) were accrued for the phase II study. The primary end point was met, with the ORR reaching 60.9% (95% CI, 45.4% to 74.9%), consisting of 1 complete response (CR), 2 CRs in target lesions, 25 partial responses, 18 responses of stable disease, 2 unevaluable responses. Median progression-free survival was 20.7 months (95% CI, 11.3 to 27.4 months). Median overall survival was not reached at the median follow-up of 28.3 months. The most common treatment-related grade 3 toxicities were hypertension and proteinuria. There were two grade 4 toxicities: duodenal ulcer and hyponatremia. Presence of tumor-infiltrating T cells, but not programmed death-ligand 1 expression, in tumor tissue correlated with response.

CONCLUSION The combination of 200 mg of pembrolizumab and a 15 mg/kg dose of bevacizumab given every 3 weeks is safe and active in metastatic RCC.

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INTRODUCTION

Abnormal tumor vasculature contributes to immune tolerance of tumor cells by impeding homing of cytotoxic T cells into tumor and their antitumor activity.¹ Tumor environment causes accumulation and subsequent polarization of myeloid-derived suppressor cells (MDSCs),² tumor-associated macrophages (TAMs),³ and dendritic cells⁴ toward immunosuppressive phenotypes. Anti-angiogenic treatment has been shown to decrease the number of MDSCs, increase the number of TAMs polarized to an immunostimulatory phenotype, and facilitate tumor infiltration by CD4⁺ and CD8⁺ T cells.⁵

The programmed death-1 (PD-1) receptor is expressed on activated T and B cells.⁶ Its major ligand, programmed death-ligand 1 (PD-L1), is expressed on a subset of macrophages but can be induced in a variety of tissues.⁷ When activated T cells expressing PD-1 encounter PD-L1, T-cell functions are diminished.^{8,9}

Multiple tumor types have been shown to express PD-L1, effectively co-opting a native tolerance.¹⁰⁻¹²

Pembrolizumab (MK-3475) is a humanized monoclonal immunoglobulin G4-κ isotype antibody against PD-1 that blocks immunoregulatory signaling of the PD-1 receptor expressed by T cells.¹³ Single-agent pembrolizumab therapy given at 200 mg intravenously every 3 weeks for 2 years or until progression showed efficacy in treatment-naïve metastatic renal cell carcinoma (mRCC) in cohort A of KEYNOTE 427, with an overall response rate (ORR) of 33.6%.¹⁴

Bevacizumab, an anti-vascular endothelial growth factor (VEGF) antibody is approved for mRCC treatment in combination with interferon alfa-2a (IFNα-2a) on the basis of two randomized phase III studies. In the AVOREN study,¹⁵ ORR was 31% for the IFNα-2a and bevacizumab arm v 13% in the IFNα-2a arm. The addition of bevacizumab was associated with an improvement in progression-free survival (PFS) and

ASSOCIATED CONTENT

Data Supplement Protocol

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

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a trend toward improvement in overall survival (OS). The CALGB 90206 trial¹⁶ showed an ORR of 25.5% for the IFN α -2a and bevacizumab arm v 13.1% in the IFN α -2a arm.

We hypothesized that the combination of bevacizumab and pembrolizumab would result in enhanced antitumor clinical activity compared with historical activity of anti-PD-1/PD-L1–blocking antibodies in mRCC.¹⁷ We conducted a phase Ib/II trial to establish first the safe dose of bevacizumab and pembrolizumab for patients with clear cell mRCC after failure of at least one systemic therapy and then, to assess efficacy and toxicity of this combination in patients with treatment-naïve mRCC.

PATIENTS AND METHODS

Study Design and Participants

This multicenter phase Ib/II clinical trial (BTCRC-GU14-003) of patients with metastatic, predominantly clear cell histology RCC was conducted through the BIG TEN Cancer Research Consortium. The phase Ib portion was conducted according to a standard 3 + 3 dose escalation design where if there was no dose-limiting toxicity (DLT) in first 3 patients at a bevacizumab dose of 10 mg/kg in combination with a fixed 200-mg dose of pembrolizumab, the next cohort of patients received a bevacizumab dose of 15 mg/kg in combination with the 200-mg dose of pembrolizumab. Both drugs were given intravenously in cycles of 3 weeks. Treatment was given until disease progression, unacceptable toxicity, or patient withdrawal. Once the maximum tolerated dose (MTD) of bevacizumab for the combination was identified, the cohort was expanded to 10 patients to ensure safety. Then, the phase II portion at that dose was open to accrual.

Patients were eligible for enrollment in the phase Ib portion of the trial if they had mRCC after experiencing failure of at least one prior systemic therapy. In the phase II portion of the study, eligible patients were treatment naïve. Patients were required to have measurable disease according to RECIST version 1.1 (v1.1)¹⁸ and adequate organ function within 14 days of starting therapy. The complete list of inclusion and exclusion criteria can be found in the study protocol (Data Supplement, online only).

The institutional review board at all participating centers approved the study protocol. All patients provided informed consent before study interventions were initiated.

Outcomes

The primary objective of the phase Ib portion was determining MTD, the safety, and DLTs of the combination. The primary objective of the phase II portion was objective ORR, as measured by RECIST v1.1. Secondary objectives included PFS and OS.

Bevacizumab was sourced from a commercial supply, and pembrolizumab was provided by Merck & Co. Bevacizumab

and pembrolizumab were infused intravenously over approximately 30 and 60 minutes, respectively, on day 1 of every 21-day cycle and administered 15-30 minutes apart. Treatment continued until disease progression, unacceptable toxicity, withdrawal of informed consent, or patient's death.

The study definition of DLT is provided in the study protocol (Data Supplement). The MTD was defined as the dose level below the dose that induced DLTs in at least one third of the patients. If an MTD was not determined, the highest tested dose level (200 mg pembrolizumab and 15 mg/kg bevacizumab) was defined as the recommended phase II dose.

Imaging of the chest, abdomen, and pelvis was performed every 6 weeks through cycle 9; thereafter, it was performed every 9 weeks. Response was assessed per the RECIST v1.1¹⁸ and immune-related RECIST.¹⁹ Toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; version 4.0).

Exploratory Studies

Expression of PD-L1 in archived diagnostic tumor tissue was determined by immunohistochemistry (IHC) using a 22C3 antibody (Qualtek Electronics, Newton, PA). Both a modified percent score (percentage of tumor and any tumor-infiltrating mononuclear inflammatory cells that had membrane staining at 1+ intensities or greater) and a modified histologic score (percentage of cells staining at either no [< 1], low [1+], moderate [2+], or high [3+] intensity) were calculated for every sample.

Tumor vascular density and CD8⁺ cell infiltration of archived diagnostic tumor tissue was determined by IHC at the University of Illinois at Chicago (UIC). Enumeration of circulating tumor cells (CTCs) at baseline and during treatment was performed in the laboratory of Seungpyo Hong, MD, at the UIC College of Pharmacy using CapiroCyte CTC capture surfaces (Capiro Biosciences, Madison, WI) with antibodies against epithelial cell adhesion molecule and epidermal growth factor receptor and rolling domains containing E-selectin, similarly to a previously described method.²⁰

PD-L1 protein levels in serum were determined using the CHECKMARK (Martell Diagnostic Laboratories, Roseville, MN) enzyme-linked immunosorbent assay (ELISA) using paired mouse monoclonal antibodies against the extracellular domain of human PD-L1. VEGF-C at baseline and during treatment was measured by Human VEGF-C Quantikine ELISA Kit (R&D Systems, Minneapolis, MN). Details of the method used to quantify tumor vascular density, CD8⁺ infiltration, CTCs, and levels of serum PD-L1 can be found in the Data Supplement.

PD-L1 expression by IHC, tumor vascular density, and CD8⁺ cell infiltration in tumor tissue were tested for association with the ORR, PFS, and OS using logistic regression

and Cox regression models, respectively. Baseline and change in serum PD-L1 and VEGF-C levels during therapy relative to baseline were examined in relation to the best clinical response and PFS. All analyses were done using SAS 9.4 software (SAS Institute, Cary, NC).

Statistical Analysis

In the phase Ib portion of the trial, a standard 3 + 3 design was used. In the phase II portion of the trial, the study end point was objective ORR (partial response [PR] or complete response [CR]) as assessed by RECIST v1.1.¹⁸ Prior studies had identified ORR with single-agent anti-PD-1 antibody of 27% in kidney cancer.¹⁷ With assumptions of 80% power to detect a 55% improvement in response to the combination over historic data on single anti-PD-1 agent activity in mRCC and a 2-sided type I error of 0.107, 48 patients were required to detect a 55% improvement to an ORR of 42%. The ORR and 95% CI were computed using SAS 9.4 software. Kaplan-Meier analysis was used to calculate PFS and OS with associated 95% CIs in both phases of the study. The effect of sex, Heng risk groups, presence of bone metastases, and prior nephrectomy status on ORR and PFS was analyzed using logistic and Cox regression models. The proportion of patients with each grade of adverse events as defined by CTCAE (version 4) was computed along with the 95% CI and reported in a tabular and descriptive manner.

RESULTS

Patient Characteristics

Thirteen patients (3 at 10 mg/kg and 10 at 15 mg/kg of bevacizumab) were enrolled in phase Ib, all of whom had received multiple lines of prior therapy (median age, 55 years; range, 33-68 years). Prior therapies included high-dose interleukin 2, pazopanib, axitinib, sunitinib, sorafenib, everolimus, and temsirolimus. No patient received prior immune checkpoint inhibitor (ICI) therapy. Forty-eight treatment-naïve patients were enrolled in the phase II portion of the study (median age, 61 years; range, 42-84 years). One patient did not receive any dose of either drug and was not included in the evaluation for PFS or OS. [Table 1](#) lists the patient characteristics.

Treatment Efficacy and Duration

In the phase Ib portion of study, the safe doses of bevacizumab 15 mg/kg and pembrolizumab 200 mg every 3 weeks were established. ORR in phase Ib was 41.7% (95% CI, 15.2% to 72.3%); 1 patient had progressive disease (PD), 6 had stable disease (SD), 5 had PRs, and 1 was not evaluable. In the phase II portion, the study's primary end point of ORR was reached at 60.9% (95% CI, 45.4% to 74.9%) with median time on treatment of 298 days (range, 21-1,113 days). Best responses in phase II were as follows: 1 CR, 2 CRs in target lesions, 25 PRs, 18 SD, and 2 unevaluable. Patients with favorable-risk disease had an ORR of 66.7%, and patients with intermediate and poor risk prognosis had an ORR of 59.5%.

TABLE 1. Patient Characteristics

Characteristic	Phase Ib, No. (%)	Phase II, No. (%)
No. of patients	13	48
Age, years		
Median	55	61
Range	33-68	42-84
Sex		
Male	11 (84.6)	33 (68.8)
Female	2 (15.4)	15 (31.3)
Ethnicity		
Hispanic or Latino	0 (0.0)	5 (10.4)
Non-Hispanic	10 (76.9)	38 (79.2)
Unknown	3 (23.1)	5 (10.4)
Race		
White	10 (76.9)	45 (93.8)
Unknown	3 (23.1)	3 (6.3)
Karnofsky PS		
70	2 (15.4)	3 (6.3)
80	3 (23.1)	10 (20.8)
90	1 (7.7)	20 (41.7)
100	7 (53.9)	15 (31.3)
Prior nephrectomy		
Yes	11 (84.6)	43 (89.6)
No	2 (15.4)	5 (10.4)
Bone metastases		
Yes	6 (46.2)	10 (20.8)
No	7 (53.8)	38 (79.2)
mRCC prognosis (by IMDC/Heng score)		
Favorable	5 (38.5)	10 (20.8)
Intermediate	3 (23.1)	31 (64.6)
Poor	5 (38.5)	7 (14.6)

Abbreviations: IMDC, International Metastatic Renal Cell Carcinoma Database; mRCC, metastatic renal cell carcinoma; PS, performance status.

[Figures 1A](#) and [1B](#) show responses to and duration of treatment in the phase Ib and phase II studies. Neither sex nor the following factors had a significant effect on likelihood of response: Heng risk groups, presence of bone metastases, or prior nephrectomy.

Median time to response was 84 days (range, 35-544 days), and median duration of response was 832 days (95% CI, 517 to 1,049 days). Median duration of pembrolizumab and bevacizumab treatment in the phase Ib study was 6.0 months (interquartile range [IQR], 2.8-10.1 months) and 10 months (IQR, 4.6-18.8 months) in the phase II study. Overall, patients received full planned doses of both drugs; median dose was 200 mg pembrolizumab

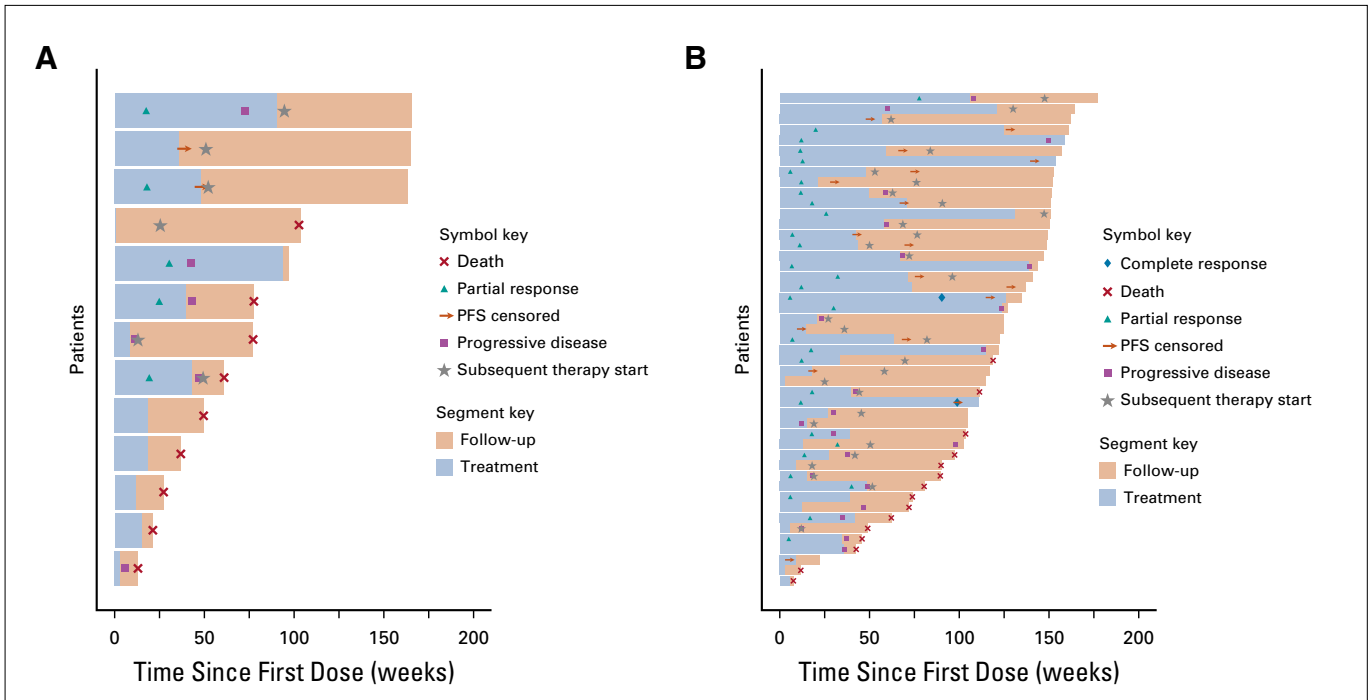


FIG 1. Swimmer plots of responses to and duration of treatment in the (A) phase Ib and (B) phase II portions of the study. PFS, progression-free survival.

and 15 mg/kg bevacizumab per cycle in both portions of the study.

PFS and OS

In the phase Ib study, median PFS was 9.9 months (95% CI, 4.9 to 16.7 months). Median OS was 17.9 months (95% CI, 6.3 months to upper limit not estimable). Both calculations were performed when the majority of events occurred (11 for PFS and 9 for OS).

In the phase II study, median PFS was estimated to be 20.7 months (95% CI, 11.3 to 27.4 months). Figure 2A shows the Kaplan-Meier curve for PFS. Neither sex nor Heng risk groups, presence of bone metastases, prior nephrectomy, and PD-L1 expression in tumor had a significant effect on PFS or OS. Median OS at 28.3 months was

not reached (only 15 of 47 died; Fig 2B). Patients with Heng favorable-risk prognosis had a median PFS of 24.8 months (95% CI, 2.8 to 32.0 months). Patients with intermediate- and poor-risk scores had a PFS of 20.68 months (95% CI, 11.31 to 27.35 months). There was no difference in PFS between favorable- and intermediate-/poor-risk patients (hazard ratio [HR] for favorable risk, 1.15; 95% CI, 0.47 to 2.83; $P = .76$).

Safety and Adverse Events

Safety was evaluated in all patients in the phase Ib and phase II portions of the study. Median number of 3-week treatment cycles was 13.5 (range, 1-48 cycles), which corresponded to 10.1 months (range, 1-36 months). Dose delays as a result of adverse events occurred in 20 patients

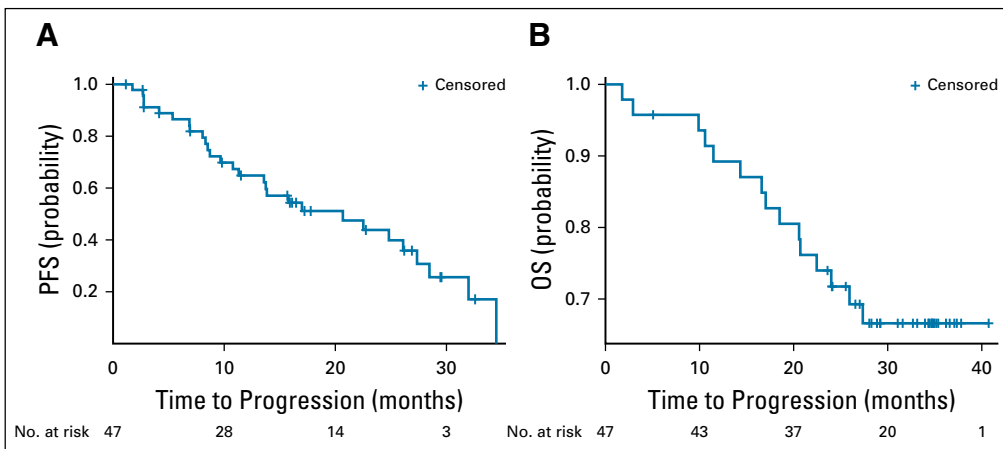


FIG 2. Kaplan-Meier curves for (A) progression-free survival (PFS) and (B) overall survival (OS).

(33.3%). The rate of treatment discontinuation because of adverse events was 33.3% (n = 20). The most common cause of treatment discontinuation was proteinuria (35%). The incidence of adverse events at least possibly related to either pembrolizumab or bevacizumab was 88.3%, and the incidence of grade 3 or 4 adverse events was 45%. The most common (> 5% incidence) treatment-related grade 3 toxicities were hypertension (25%), proteinuria (10%), adrenal insufficiency (6.7%), and pain/headaches (5.0%). There were two grade 4 toxicities (hyponatremia and duodenal ulcer). There was no grade 5 toxicities related to study treatment. Table 2 lists all the treatment-related grade 3 and 4 toxicities. There were the following grade 3 immune-related toxicities: adrenal insufficiency (6.7%); pneumonitis (3.3%); and gastritis, hepatitis, hypothyroidism, oral mucositis, and skin rash (each 1.7%; Table 3). Seventeen patients were treated with systemic steroids for immune-related toxicities. All grade > 2 adverse events in

TABLE 2. Grade 3 and 4 Adverse Events Related to Treatment

CTCAE (version 4.0) Term	Grade	Count	%
Duodenal ulcer	4	1	1.67
Hyponatremia	4	1	1.67
Hypertension	3	15	25.00
Proteinuria	3	6	10.02
Adrenal insufficiency	3	4	6.67
Pain/headaches	3	3	5.01
Pneumonitis	3	2	3.33
Hyponatremia	3	2	3.33
Generalized muscle weakness	3	2	3.33
Dehydration	3	2	3.33
Skin rashes	3	2	3.33
Anemia	3	2	3.33
Nausea	3	1	1.67
Vomiting	3	1	1.67
Thromboembolic event	3	1	1.67
Seizure	3	1	1.67
Myocardial infarction	3	1	1.67
Mucositis oral	3	1	1.67
Immune-mediated hepatitis	3	1	1.67
Immune-mediated gastritis	3	1	1.67
Hypothyroidism	3	1	1.67
Hematuria	3	1	1.67
Flu-like symptoms	3	1	1.67
Diarrhea	3	1	1.67
Arthralgia	3	1	1.67
Alkaline phosphatase increased	3	1	1.67

NOTE. n = 60.

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events.

TABLE 3. All-Grade Immune-Related Adverse Events

CTCAE (version 4.0) Term	Grade	Count	%
Adrenal insufficiency	3	4	6.67
Pneumonitis	3	2	3.33
Gastritis	3	1	1.67
Hepatitis	3	1	1.67
Hypothyroidism	3	1	1.67
Mucositis oral	3	1	1.67
Rash	3	1	1.67
Hypothyroidism	2	8	13.33
Rash	2	5	8.34
Adrenal insufficiency	2	2	3.33
Gastritis	2	2	3.33
Pneumonitis	2	2	3.33
Nephritis	2	2	3.33
Hepatitis	2	1	1.67
Hyperthyroidism	2	1	1.67
Pruritus	1	14	23.33
Rash	1	13	21.68
Mucositis oral	1	5	8.34
Hypothyroidism	1	3	5.00
Pneumonitis	1	3	5.01
Hyperthyroidism	1	2	3.33
Thyroiditis	1	1	1.67

NOTE. n = 60.

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events.

the study and adverse events that led to treatment discontinuation are listed in the Data Supplement.

Exploratory Studies

The analysis details of the correlation of exploratory end points with ORR, PFS, and OS are listed in the Data Supplement. There were no differences in ORR, PFS, and OS between groups, with expression of PD-L1 only in interface, in tumor only, in stroma and tumor, or without PD-L1 in stroma and tumor. Patients with tumor over-expressing PD-L1 > 0 had a trend toward better PFS after 20 months, but there was no statistical difference in overall PFS (P = .37). A higher level of tumor-infiltrating cells was associated with a trend of higher chance of response (HR, 1.80; 95% CI, 0.90 to 3.59; P = .096).

For evaluation of tumor vascular density and CD8+ cell infiltration, 41 samples from primary nephrectomy and 3 from metastases were available. Neither number of CD8+ cells per tumor area or per number of tumor cells nor tumor vascular density had any effect on ORR, PFS, or OS. There was no correlation between baseline CTC number and ORR or PFS. Enumeration of CTCs in subsequent blood draws significantly decreased in all samples compared with

baseline ($P = .0472$), but the degree of decline did not correlate with ORR or PFS. Similarly, neither baseline soluble PD-L1 level nor change in cycle 3 predicted ORR or PFS. There was no correlation between VEGF-C at baseline or changes in VEGF-C levels in subsequent cycles of therapy with ORR, but an increase in VEGF-C in subsequent cycles marginally increased risk of progression (HR, 1.1; 95% CI, 0.98 to 1.24; $P = .099$) and shortened OS (HR, 1.19; 95% CI, 0.99 to 1.43; $P = .062$).

DISCUSSION

There were no DLTs in the phase Ib portion of the study; in both phases, therapy was well tolerated, with patients receiving a high number of cycles (median, 13.5 cycles), which corresponds to 10 months of treatment (range, 4.6–18.8 months). The incidence of grade 3 or 4 adverse events was seen in 45% of patients, which compares favorably with other combinations of ICIs and tyrosine kinase inhibitors (TKIs), where grade 3 and 4 toxicities occurred in 65%–67% of patients.^{21,22}

The phase Ib portion of the study was done in a heavily pretreated population with multiple prior lines of therapy, yet the combination of pembrolizumab and bevacizumab had produced a substantive ORR of 41.7% (95% CI, 15.2% to 72.3%). The phase II portion of the study met its primary end point, with a high ORR of 60.9% (95% CI, 45.4% to 74.9%). The efficacy was also reflected in the median PFS of 20.7 months and in the median OS not being reached despite a median follow-up of 28.3 months.

In comparison, single-agent pembrolizumab produces an ORR of 33.6% (95% CI, 24.8% to 43.4%) in patients with RCC,¹⁴ and single bevacizumab can achieve an ORR of only 10% (95% CI, 2.9% to 24.2%).²³ The ORR and PFS in the combination are comparable to other combinations of ICIs and TKIs, but the toxicity appears to be lower in this trial. Cabozantinib in combination with atezolizumab in the COSMIC-021 study in treatment-naïve patients produced an ORR of 50% (95% CI, 12% to 88%) when 40 mg of cabozantinib was used and 83% (95% CI, 36% to 100%) when 60 mg was used. Adverse events that required a dose reduction of cabozantinib occurred in 50% of patients treated with the 40-mg dose and in 100% of patients treated with the 60-mg dose. Adverse events that led to dose interruptions occurred in 50% and 67%, respectively.²⁴ The combination of avelumab and axitinib has

been reported in phase Ib²⁵ and phase III²¹ studies, where patients treated with the combination had a median PFS of 13.8 months (reported in phase III but not in phase Ib). The ORR with this combination was 58% (phase Ib) and 51.4% (phase III) of patients. However, grade 3 and 4 treatment-related toxicity occurred in 58% (phase Ib) and 71.2% (phase III) of patients.

The activity of combination axitinib and pembrolizumab has been reported in phase Ib²² and phase III²⁶ studies. Median PFS was 20.9 and 15.1 months, respectively, and ORR was 73% and 59.3%, respectively. Grade 3/4 treatment-related toxicities were seen in 65% (phase Ib) and 62.9% (phase III) of patients.

In the CheckMate 016 study of nivolumab and either pazopanib or sunitinib, treatment-related grade 3/4 adverse events and treatment discontinuations as a result of toxicity were frequent (70% and 82% and 25% and 39%, respectively). In the sunitinib and nivolumab arm, ORR was 55%, and PFS was 12.7 months; in the pazopanib and nivolumab arm, ORR was 45%, and PFS was 7.2 months.²⁷

Activity of atezolizumab and bevacizumab was tested in randomized phase II²⁸ and III²⁹ studies. Median PFS was 11.7 and 11.2 months, and ORR was 32% and 43%, respectively. PD-L1 expression has been reported to be associated with greater activity of atezolizumab and bevacizumab²⁹ and that of nivolumab and ipilimumab,³⁰ but in our study, there was no correlation between PD-L1 tissue expression and ORR or PFS.

In patients with tumors with a preexisting presence of effector T cells, therapy with combination ICIs and VEGF inhibitors resulted in better PFS versus sunitinib.²⁸ This is concordant with our observation that a higher level of tumor-infiltrating immune cells at baseline was marginally associated with a higher chance of PR (odds ratio, 1.80; 95% CI, 0.90 to 3.59; $P = .096$).

In conclusion, the combination of pembrolizumab and bevacizumab has an acceptable toxicity profile and is active in patients with mRCC as first and subsequent lines of therapy. It could be further tested in patient populations where TKIs are not well tolerated and can cause early treatment discontinuation. With the exception of an increased number of tumor-infiltrating cells correlating with a higher likelihood of response, no predictive biomarkers in tissue or blood were identified.

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