

Open-Label, Single-Arm Phase II Study of Pembrolizumab Monotherapy as First-Line Therapy in Patients With Advanced Clear Cell Renal Cell Carcinoma

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PURPOSE Pembrolizumab, a programmed death 1 inhibitor, demonstrated promising single-agent activity in untreated patients with various cancer types. The phase II KEYNOTE-427 study evaluated efficacy and safety of single-agent pembrolizumab in treatment-naïve patients with advanced clear cell renal cell carcinoma (ccRCC; cohort A) and advanced non-ccRCC (cohort B). Results of cohort A are reported.

METHODS In this open-label, single-arm phase II study, patients with advanced ccRCC received pembrolizumab 200 mg every 3 weeks for \leq 24 months. The primary end point was objective response rate by RECIST, version 1.1.

RESULTS In the total population (N = 110), median time from enrollment to data cutoff was 35.9 (range, 29.5-40.3) months. Objective response rate was 36.4% with four (3.6%) complete responses and 36 (32.7%) partial responses; disease control rate was 58.2% (95% CI, 48.4 to 67.5). Most patients (68.2%) had a decrease in target lesions, including 30.9% with a reduction \geq 60%. Median duration of response was 18.9 (range, 2.3-37.6+) months; 64.1% of responders had a response \geq 12 months (Kaplan-Meier). Median progression-free survival was 7.1 months (95% CI, 5.6 to 11.0). Median overall survival was not reached; 12-month and 24-month overall survival rates were 88.2% and 70.8%, respectively. Durable responses were observed across all International Metastatic RCC Database Consortium categories. Grade 3-5 treatment-related adverse events were reported in 30.0% of patients, of which colitis and diarrhea were most frequent.

CONCLUSION Single-agent pembrolizumab showed promising antitumor activity as a first-line treatment in patients with advanced ccRCC, with durable responses across International Metastatic RCC Database Consortium categories. Safety and tolerability profile of pembrolizumab monotherapy was comparable to what has been previously described in other tumor types.

J Clin Oncol 39:1020-1028. © 2021 by American Society of Clinical Oncology

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ASSOCIATED CONTENT

Appendix

Protocol

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

Accepted on November 30, 2020 and published at ascopubs.org/journal/jco on February 2, 2021; DOI <https://doi.org/10.1200/JCO.20.02363>

INTRODUCTION

Recent efforts in immunotherapeutic approaches for advanced renal cell carcinoma (RCC) have focused on immune checkpoint inhibition, specifically with agents that block the programmed death 1 (PD-1) receptor and its ligands, PD-L1 and PD-L2. The PD-1 inhibitor nivolumab was approved in 2015 for use in patients whose disease progressed following prior antiangiogenic regimens, including first-line vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs), because of its overall survival (OS) benefit relative to everolimus.¹ Subsequent clinical trials evaluated anti-PD-1–based and anti-PD-L1–

based combination therapies for the first-line treatment of patients with advanced RCC, and results of those studies led to US Food and Drug Administration (FDA) approval of nivolumab plus ipilimumab, a cytotoxic T-lymphocyte antigen 4 inhibitor (CheckMate 214); pembrolizumab, a PD-1 inhibitor, plus axitinib, a TKI (KEYNOTE-426); and avelumab, a PD-L1 inhibitor, plus axitinib (JAVELIN Renal 101) in that patient population.²⁻⁴ Although PD-1 and PD-L1 inhibitor–based combination therapy is changing the front-line RCC treatment landscape, little is known about the efficacy of single-agent PD-1 or PD-L1 inhibitors in this setting. The present study aimed to investigate

CONTEXT

Key Objective

To determine if it is possible to treat patients with recurrent or advanced or metastatic clear cell renal cell carcinoma (ccRCC) who received no prior systemic anticancer therapy with pembrolizumab monotherapy.

Knowledge Generated

Pembrolizumab monotherapy demonstrated promising antitumor activity and showed acceptable safety in patients treated in the first-line setting of advanced or metastatic ccRCC. Pembrolizumab monotherapy demonstrated an objective response rate of 36.4% in the overall population, which was consistent across key subgroups including all International Metastatic RCC Database risk groups, in patients with tumors with high and low programmed death ligand 1 status, and in patients with tumors with sarcomatoid differentiation.

Relevance

These results provide support for the exploration of pembrolizumab monotherapy in the adjuvant setting and for further exploration of pembrolizumab monotherapy and novel pembrolizumab-based combination regimens in patients with advanced or metastatic ccRCC.

the efficacy and safety of the PD-1 inhibitor pembrolizumab monotherapy in patients with recurrent or advanced or metastatic ccRCC who received no prior systemic anticancer therapy.

METHODS

Study Design and Objectives

KEYNOTE-427 (ClinicalTrials.gov identifier: [NCT02853344](https://clinicaltrials.gov/ct2/show/study/NCT02853344)) was a single-arm, open-label, nonrandomized, multicenter (61 sites), global (10 countries) phase II trial. The study was conducted in accordance with International Conference on Harmonization guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. The Protocol was approved by the institutional review board or independent ethics committee for each participating institution. All patients provided written informed consent.

Pembrolizumab was administered at a dose of 200 mg intravenously every 3 weeks. Study treatment was continued until confirmed progressive disease (PD); unacceptable toxicity or intercurrent illness that prevented further administration of treatment; 35 doses of pembrolizumab had been received; or withdrawal of consent, whichever occurred first. Following identification of radiologic PD by the investigator, clinically stable patients were permitted to remain on study treatment while waiting for investigator-determined PD confirmation (irRECIST) by means of follow-up imaging at ≥ 4 weeks after first PD observation.

Patient Characteristics

Adult patients (≥ 18 years of age) with locally advanced or metastatic, histologically confirmed ccRCC were included in the study. Patients were required to have measurable disease per RECIST, version 1.1 (RECIST v1.1); a Karnofsky performance status score ≥ 70 ; and adequate organ function. Patients were not permitted to have previously received systemic therapy for advanced or metastatic RCC.

Prior neoadjuvant or adjuvant therapy for RCC was acceptable if completed > 12 months before allocation. Patients were required to provide tissue samples for biomarker analysis.

Use of systemic steroid therapy exceeding 10 mg daily dose of prednisone or equivalent or any other form of immunosuppressive therapy within 7 days before allocation was not permitted. Patients with active CNS metastases and/or carcinomatous meningitis, current pneumonitis or history of noninfectious pneumonitis, active infection requiring systemic therapy, active hepatitis C, or history of hepatitis B or HIV infection were excluded from participation in the study.

Study Assessments

The primary end point was objective response rate (ORR), as assessed per RECIST v1.1 by blinded independent central review. Secondary end points were duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS) per RECIST v1.1 as assessed by blinded independent central review, OS, and safety and tolerability. Exploratory end points included ORR, DOR, and DCR in relation to (1) PD-L1 status, (2) International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) RCC risk status,⁵ and (3) presence of any sarcomatoid differentiation.

Imaging assessments included computed tomography and/or magnetic resonance imaging of the chest, abdomen, and pelvis and were performed at baseline, at week 12, then every 6 weeks until week 54, and every 12 weeks thereafter. Patients with initial evidence of PD by RECIST v1.1 continued study treatment (if clinically stable) at the discretion of the investigator until repeat imaging (irRECIST) ≥ 4 weeks later was obtained by the investigator. Study treatment could be continued beyond confirmed disease progression provided patients were deriving a clinical benefit, as assessed by investigator, and upon consultation with the sponsor. Baseline bone scans were

performed at screening; at weeks 18, 30, 42, and 54, and then every 24 weeks thereafter. A bone scan was required for confirmation of a complete response (CR). PD-L1 expression was assessed using the PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Santa Clara, CA) assay, and “PD-L1-positive” was defined as a combined positive score (CPS) ≥ 1 . CPS was calculated as the ratio of numbers of tumor cells, lymphocytes, and macrophages expressing PD-L1 to the total number of viable tumor cells in the biopsy specimen $\times 100$. Sarcomatoid differentiation was evaluated by local pathologist and captured in the electronic database. Adverse events (AEs) were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, and monitored throughout the study and for 30 days after the last dose of pembrolizumab (≤ 90 days for serious AEs and > 90 days for serious treatment-related AEs).

Statistical Analyses

ORR was calculated as the proportion of patients in the analysis population (all patients as treated) who had a CR or partial response (PR). The 95% CI for ORR was calculated using the Clopper-Pearson method based on binomial distribution. Final response assessments were determined by a central adjudication process that took all imaging results into consideration. The Kaplan-Meier method for censored data was used to estimate OS, PFS, and DOR from the date of the first exposure to pembrolizumab to the database cutoff date. Efficacy and safety were assessed in all treated patients. Because no statistical comparisons were made, no statistical adjustments were performed. Database cutoff was February 24, 2020.

RESULTS

Patient Disposition and Baseline Demographics

Median time from enrollment to data cutoff was 35.9 (range, 29.5-40.3) months. Most patients in the study population ($n = 110$) were male (78.2%), and median age was 64 (range, 29-87) years. Most patients resided either in North America (40.9%) or Western Europe (33.6%) and had a Karnofsky performance status score between 90 and 100 (80.0%) (Table 1). The PD-L1 expression status was CPS ≥ 1 in 47.3% ($n = 52$) of study participants. Forty-two (38.2%) and 68 (61.8%) patients were classified in favorable and intermediate or poor IMDC risk categories, respectively.

At analysis, 20 patients had completed 2 years of treatment and 90 discontinued treatment (Appendix Fig A1, online only). The most common reasons for treatment discontinuation were radiologic disease progression ($n = 53$) and AEs ($n = 24$; 17 patients discontinued because of treatment-related AEs). Other reasons for discontinuation included clinical progression ($n = 6$), treatment with other anticancer therapy ($n = 2$), patient withdrawal ($n = 2$), physician decision ($n = 1$), and CR ($n = 1$). Sixty percent

TABLE 1. Baseline Characteristics

Characteristic, n (%)	N = 110
Sex	
Male	86 (78.2)
Female	24 (21.8)
Age, years	
Median (range)	64 (29-87)
< 65	58 (52.7)
≥ 65	52 (47.3)
Geographic region	
North America	45 (40.9)
Western Europe	37 (33.6)
Rest of world	28 (25.5)
KPS score	
90-100	88 (80.0)
70-80	22 (20.0)
IMDC risk categories	
Favorable	42 (38.2)
Intermediate or poor	68 (61.8)
PD-L1 status	
CPS ≥ 1	52 (47.3)
CPS < 1	58 (52.7)
Sites of metastatic disease	
Lung	76 (69.1)
Lymph node	51 (46.4)
Bone	23 (20.9)
Adrenal gland	17 (15.5)
Liver	19 (17.3)
Prior nephrectomy	92 (83.6)

Abbreviations: CPS, combined positive score; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; KPS, Karnofsky Performance Status; PD-L1, programmed death ligand 1.

($n = 66$) of patients received subsequent anticancer therapy, and most of those patients received a VEGF or VEGFR inhibitor ($n = 59$).

Efficacy Outcomes in the Total Population

The ORR was 36.4% (95% CI, 27.4 to 46.1) in the overall study cohort ($n = 110$), with four CRs (3.6%) and 36 PRs (32.7%) (Table 2). The analysis of the change from baseline in target lesions showed that 68.2% (75/110) of patients had a reduction in tumor burden; 46.4% (51/110) had reductions $\geq 30\%$, 30.9% (34/110) had reductions $\geq 60\%$, 19.1% (21/110) had reductions $\geq 80\%$, and 7.3% (8/110) had reductions of 100% (Fig 1). Thirty-five (31.8%) patients had stable disease at first imaging, and 24 patients (21.8%) had stable disease for ≥ 6 months. DCR, defined

TABLE 2. ORR per Blinded Independent Central Review in the Total Population and by Patient Subgroups

Parameter	Total Population	IMDC Category		PD-L1 Expression		Sarcomatoid Differentiation
	N = 110	Favorable n = 42	Intermediate or Poor n = 68	CPS ≥ 1 n = 52	CPS < 1 n = 58	n = 11
ORR, % (95% CI)	36.4 (27.4 to 46.1)	31.0 (17.6 to 47.1)	39.7 (28.0 to 52.3)	44.2 (30.5 to 58.7)	29.3 (18.1 to 42.7)	63.6 (30.8 to 89.1)
DCR (CR + PR + SD ≥ 6 mo), % (95% CI)	58.2 (48.4 to 67.5)	61.9 (45.6 to 76.4)	55.9 (43.3 to 67.9)	63.5 (49.0 to 76.4)	53.4 (39.9 to 66.7)	72.7 (39.0 to 94.0)
Best response, n (%)						
CR	4 (3.6)	1 (2.4)	3 (4.4)	3 (5.8)	1 (1.7)	0 (0)
PR	36 (32.7)	12 (28.6)	24 (35.3)	20 (38.5)	16 (27.6)	7 (63.6)
SD	35 (31.8)	21 (50.0)	14 (20.6)	16 (30.8)	19 (32.8)	2 (18.2)
PD	33 (30.0)	8 (19.0)	25 (36.8)	12 (23.1)	21 (36.2)	2 (18.2)
No assessment ^a	2 (1.8)	0 (0)	2 (2.9)	1 (1.9)	1 (1.7)	0 (0)

Abbreviations: CPS, combined positive score; CR, complete response; DCR, disease control rate; IMDC, International Metastatic RCC Database Consortium; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death ligand 1; PR, partial response; SD, stable disease.

^aIncludes patients who discontinued treatment or died before the first baseline scan.

as the sum of patients with CRs, PRs, and stable disease lasting ≥ 6 months, was 58.2% (95% CI, 48.4 to 67.5).

The median time to response was 2.8 months (range, 2.5-12.9 months). The median DOR was 18.9 months (range, 2.3-37.6 + months) and, by Kaplan-Meier estimate, 64.1% of responses were maintained for ≥ 12 months and 58.3% had a response for ≥ 18 months (Fig 2A). Of 40 patients who experienced a response (CR or PR), 18 completed 2 years of treatment (Fig 2B). At data cutoff, 15 patients had an ongoing response and 21 later experienced a subsequent PD. Two patients were censored for missing at least two consecutive disease assessments, one patient was censored for response duration because of starting a new anticancer therapy without documented PD, and one patient did not have adequate assessments at the time of data cutoff.

Median PFS was 7.1 months (95% CI, 5.6 to 11.0; Fig 3A) with a 12-month PFS rate of 37.6% and a 24-month PFS rate

of 22.3%. The 12- and 24-month OS rates were 88.2% and 70.8%, respectively; median OS was not reached (Fig 3B).

Efficacy Outcomes by IMDC Risk Category

For patients with favorable IMDC risk (n = 42), ORR was 31.0% (95% CI, 17.6 to 47.1) with one CR (2.4%) and 12 PRs (28.6%; Table 2). DCR was 61.9% (95% CI, 45.6 to 76.4). Median DOR was 18.2 months (range, 4.2-37.6 + months), and by Kaplan-Meier estimate, 61.5% had a response ≥ 12 months (Appendix Fig A2, online only). Median PFS was 9.7 months (95% CI, 5.6 to 12.4); 12-month PFS rate was 40.9% and 24-month PFS rate was 19.1%. The 12- and 24-month OS rates were 97.6% and 88.0%, respectively.

In the intermediate or poor IMDC risk group (n = 68), the ORR was 39.7% (95% CI, 28.0 to 52.3) with three CRs (4.4%) and 24 PRs (35.3%; Table 2). DCR was 55.9% (95% CI, 43.3 to 67.9). Median DOR was not reached (range, 2.3-34.3 + months); by Kaplan-Meier estimate, DOR ≥ 12 months was 65.5% (Appendix Fig A2, online only). Median PFS was 6.9 months (95% CI, 3.3 to 11.0); 12-month PFS rate was 35.5% and 24-month PFS rate was 24.4%. The 12- and 24-month OS rates were 82.4% and 60.3%, respectively.

Efficacy Outcomes by PD-L1 Expression

For patients with CPS ≥ 1 (n = 52), ORR was 44.2% (95% CI, 30.5 to 58.7; Table 2). Median DOR was 18.2 months (95% CI, 2.8 to 34.3 + months) and DOR ≥ 12 months was 65.2% by Kaplan-Meier estimate. Median PFS was 9.7 months (95% CI, 6.7 to 16.3 months), and 12- and 24-month PFS rates were 40.3% and 26.2%, respectively. Median OS was not reached; the 12- and 24-month OS rates were 92.3% and 78.7%, respectively.

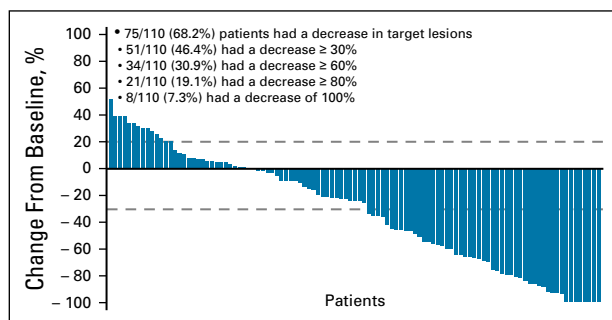


FIG 1. Maximum change from baseline in target lesions by central review. Patients who received ≥ 1 dose of pembrolizumab had a baseline scan with measurable disease and had a postbaseline assessment (n = 107).

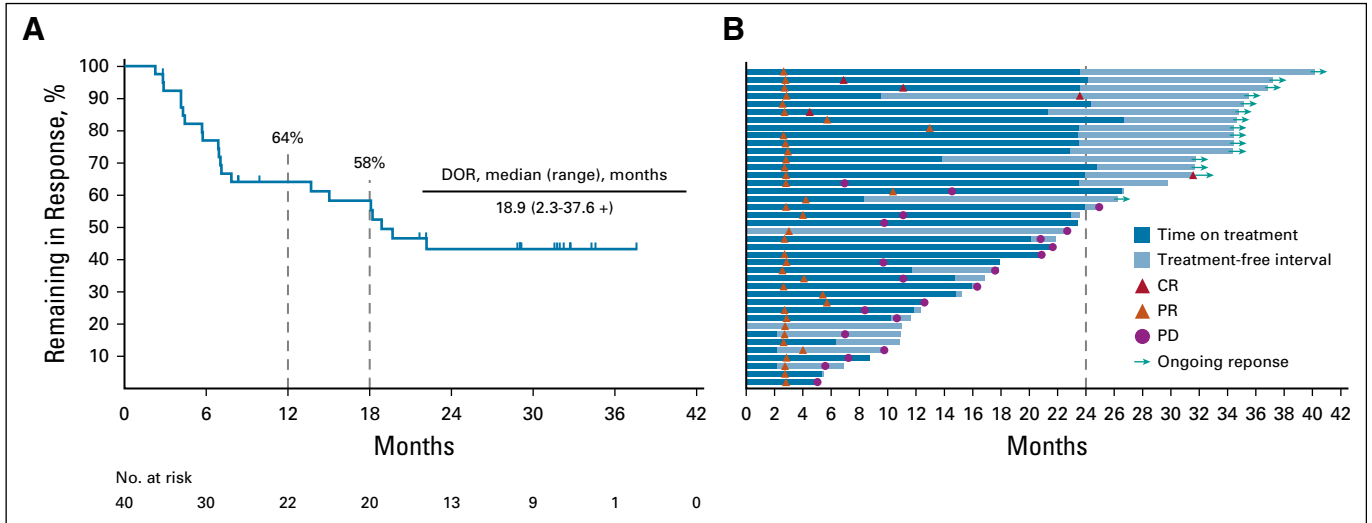


FIG 2. Kaplan-Meier estimate of duration of response (A) and time to response and duration of response (B). CR, complete response; DOR, duration of response; PD, progressive disease; PR, partial response.

For patients with CPS < 1 (n = 58), ORR was 29.3% (95% CI, 18.1 to 42.7; Table 2). Median DOR was 19.7 months (95% CI, 2.3 to 37.6); by Kaplan-Meier estimate, 62.7% had a DOR ≥ 12 months. Median PFS was 6.9 months (95% CI, 3.3 to 10.9); 12- and 24-month PFS rates were 35.3% and 18.7%, respectively. Median OS was not reached; 12- and 24-month OS rates were 84.5% and 63.7%, respectively.

Efficacy Outcomes by Sarcomatoid Differentiation

Among patients with sarcomatoid differentiation (n = 11), ORR was 63.6% (95% CI, 30.8 to 89.1; Table 2); DCR was 72.7%. Median DOR was 15.0 (95% CI, 5.7 to 37.6 +) months and 71.4% had a response ≥ 12 months by Kaplan-Meier estimate. Median PFS was 16.3 months

(95% CI, 3.0 to 21.6), and the 12- and 24-month PFS rates were 53.0% and 21.2%, respectively. Median OS was 32.2 months (95% CI, 11.8 to NR); the 12- and 24-month OS rates were 81.8% and 63.6%, respectively.

Safety and Tolerability

One or more treatment-related AEs of any grade were recorded in 82.7% of study patients (n = 91; Table 3). Seventeen treatment-related AEs were recorded at a frequency ≥ 5% in the study cohort. Pruritus (30.0%), fatigue (29.1%), diarrhea (22.7%), rash (19.1%), arthralgia (14.5%), and hypothyroidism (12.7%) were the most frequently reported treatment-related AEs (any grade). Grade 3-5 treatment-related AEs were recorded in 30.0% of patients; colitis (5.5%) and diarrhea (3.6%) were the most

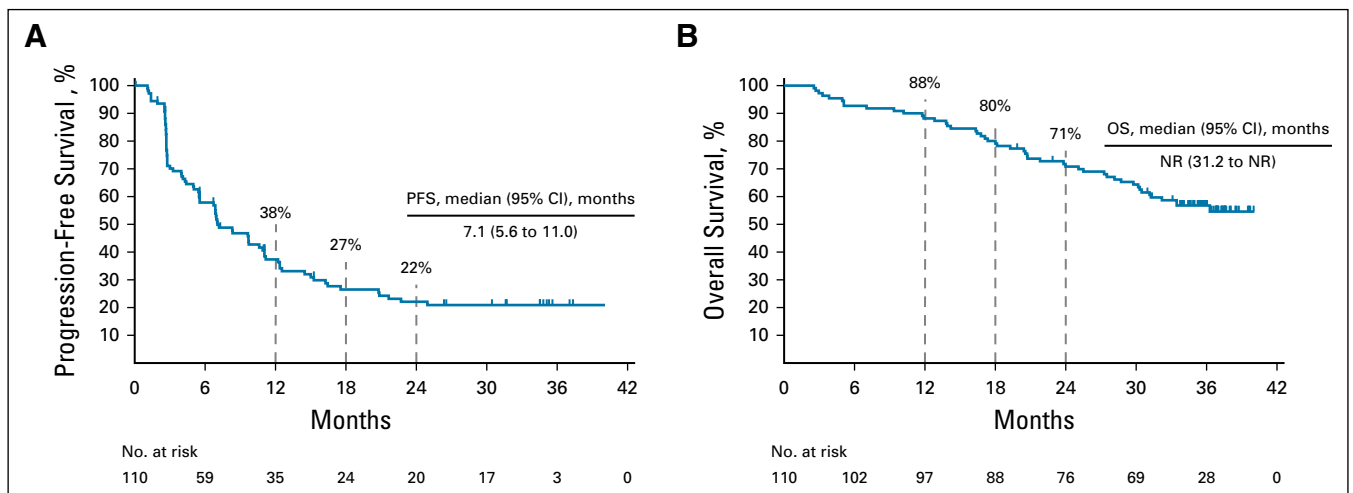


FIG 3. Kaplan-Meier estimates of (A) progression-free survival based on central radiology assessment per RECIST v1.1 and (B) overall survival. NR, not reached; OS, overall survival; PFS, progression-free survival.

TABLE 3. Incidence of Treatment-Related and Immune-Mediated^a AEs of Any Grade and of Corresponding Grade 3-5 AEs

Adverse Event	N = 110	
	Any Grade (≥ 2 Patients)	Grade 3-5
Any, n (%)	91 (82.7)	33 (30.0)
Pruritus	33 (30.0)	0 (0.0)
Fatigue	32 (29.1)	2 (1.8)
Diarrhea	25 (22.7)	4 (3.6)
Rash ^b	21 (19.1)	2 (1.8)
Arthralgia	16 (14.5)	1 (0.9)
Hypothyroidism	14 (12.7)	0 (0.0)
ALT increased	9 (8.2)	1 (0.9)
Decreased appetite	9 (8.2)	0 (0.0)
AST increased	8 (7.3)	2 (1.8)
Asthenia	8 (7.3)	3 (2.7)
Dry mouth	7 (6.4)	0 (0.0)
Influenza-like illness	7 (6.4)	0 (0.0)
Nausea	7 (6.4)	0 (0.0)
Colitis	6 (5.5)	6 (5.5)
Dyspnea	6 (5.5)	0 (0.0)
Hyperthyroidism	6 (5.5)	0 (0.0)
Myalgia	5 (4.5)	2 (1.8)
Pneumonitis	5 (4.5)	1 (0.9) ^c
Constipation	4 (3.6)	0 (0.0)
Dry skin	4 (3.6)	0 (0.0)
Hyperglycemia	4 (3.6)	2 (1.8)
Mucosal inflammation	4 (3.6)	0 (0.0)
Pyrexia	4 (3.6)	1 (0.9)
Vomiting	4 (3.6)	0 (0.0)
Abdominal pain	3 (2.7)	0 (0.0)
Anemia	3 (2.7)	0 (0.0)
Blood alkaline phosphatase increased	3 (2.7)	1 (0.9)
Blood creatinine increased	3 (2.7)	0 (0.0)
Lymphocyte count decreased	3 (2.7)	0 (0.0)
Peripheral neuropathy	3 (2.7)	1 (0.9)
Acute kidney injury	2 (1.8)	0 (0.0)
Contrast media allergy	2 (1.8)	1 (0.9)
Dry eye	2 (1.8)	0 (0.0)
Headache	2 (1.8)	0 (0.0)
Hepatitis	2 (1.8)	2 (1.8)
Hyponatremia	2 (1.8)	2 (1.8)
Hypophosphatemia	2 (1.8)	2 (1.8)
Myositis	2 (1.8)	1 (0.9)

(continued in next column)

TABLE 3. Incidence of Treatment-Related and Immune-Mediated^a AEs of Any Grade and of Corresponding Grade 3-5 AEs (continued)

Adverse Event	N = 110	
	Any Grade (≥ 2 Patients)	Grade 3-5
Immune-mediated AEs, n (%)		
Any	36 (32.7)	17 (15.5)
Hypothyroidism	15 (13.6)	0
Colitis	7 (6.4)	6 (5.5)
Hyperthyroidism	6 (5.5)	0
Pneumonitis	5 (4.5)	1 (0.9) ^c
Severe skin reaction	3 (2.7)	3 (2.7)
Adrenal insufficiency	2 (1.8)	2 (1.8)
Hepatitis	2 (1.8)	2 (1.8)
Myositis	2 (1.8)	1 (0.9)
Pancreatitis	2 (1.8)	2 (1.8)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase.

All cases of adrenal insufficiency, colitis, hepatitis, myositis, pneumonitis, and severe skin reactions were treated with corticosteroids. Two cases of grade 3/4 pancreatitis did not require treatment with corticosteroids.

^aBased on a list of terms specified by the sponsor and included by the investigator regardless of attribution to study treatment or immune relatedness.

^bIncludes maculopapular rash and macular rash.

^cGrade 5 pneumonitis.

frequent (Table 3). Thirty-six patients experienced 50 episodes of immune-related AEs, with hypothyroidism, colitis, and hyperthyroidism being the most common in 13.6%, 6.4%, and 5.5% of patients, respectively. Twenty-four (44.4%) immune-related AE episodes were managed with a high starting dose of corticosteroids (≥ 40 mg/d prednisone or equivalent), 4 episodes (7.4%) were managed with a low starting dose of corticosteroids (< 40 mg/d), and 26 episodes did not require corticosteroid treatment. Three patients died because of AEs. One patient died of treatment-related pneumonitis; the other two deaths (cerebral infarction and intracranial hemorrhage) were not considered treatment related.

DISCUSSION

To our knowledge, KEYNOTE-427 is the first study to date to evaluate the clinical utility of a single-agent PD-1 inhibitor in a large cohort of previously untreated patients with advanced ccRCC. In this single-arm phase II trial, pembrolizumab monotherapy showed promising antitumor activity in the overall population (ORR, 36.4%; CR, 3.6%; PR, 32.7%) and across key subgroups that included all IMDC risk groups, and in patients with tumors with high and low PD-L1 status, and patients with tumors with sarcomatoid differentiation. Fifteen of 40 responding patients experienced ongoing responses at data cutoff. The median

DOR was 18.9 months and 64.0% of responders maintained their response for at least 12 months, and the 24-month OS rate was 70.8%. Taken together, these results show that pembrolizumab monotherapy has durable antitumor activity in untreated patients with advanced ccRCC.

The safety profile of pembrolizumab monotherapy in the current study is comparable to the previously observed safety profiles of pembrolizumab in other tumor types.⁶ Commonly reported grade 3/4 treatment-related AEs associated with pembrolizumab monotherapy were colitis (6.4%) and diarrhea (3.6%), and 17 (15.5%) patients discontinued treatment because of treatment-related AEs. One patient died of treatment-related pneumonitis. Immune-mediated AEs, including hypothyroidism, colitis, rash, and pneumonitis, have been reported to occur with PD-1 or PD-L1 inhibitor therapy.⁷ Guidelines for managing immune-related AEs recommend corticosteroid treatment for grade 2-4 events, holding immunotherapy until grade 2/3 events return to grade 1, and discontinuing immunotherapy for grade 4 events.⁸ In the current study, 28 of 54 immune-related AE episodes required concomitant corticosteroid use with a high starting dose (≥ 40 mg/d prednisone or equivalent) being chosen to manage 24 of the events.

Although the measurement of PD-L1 expression in the tumor microenvironment by immunohistochemistry has been shown to be predictive of response to anti-PD-1 agents in some cancer types (eg, non-small-cell lung cancer), there is currently no definitive predictive biomarker in RCC.⁹ Results of the current study showed that a higher percentage of patients with tumors of CPS ≥ 1 than CPS < 1 experienced CRs and PRs, which resulted in a higher ORR in patients with tumor CPS ≥ 1 (44.2 v 29.3%); however, a sizable proportion of patients with tumor CPS < 1 still experienced tumor response. A high percentage of patients with sarcomatoid RCC had an objective response (ORR, 63.6%), but the sample size was small. Recent correlative studies associated with randomized trials have suggested that tumor histology (eg, sarcomatoid) and DNA and RNA analyses of the tumor microenvironment may sharpen our ability to predict response to PD-1 or PD-L1 inhibitor-based combination therapy.¹⁰⁻¹² Future analysis of KEYNOTE-427 will evaluate biomarkers associated with response to pembrolizumab monotherapy. Given that, the data from this study and others suggest that the development of a predictive model that examines both tumor and immune infiltrate may be possible to help guide clinical decision making in patients with advanced RCC.

Other primary tumor sites, such as lung cancer, have observed greater activity with checkpoint inhibitor immunotherapy in the first-line relative to the second-line setting.¹³ This difference between first-line and second-line checkpoint inhibitor activity was likely observed with our study when compared with studies of other PD-1 inhibitors in RCC in the second-line setting.¹ These differences may be the result of treatment settings, as patients treated after

VEGFR TKIs may have relatively few immune responsive tumors (eg, those with sarcomatoid histology), or of the distinct levels of activity of the agents tested. Additionally, there appeared to be differences in efficacy between our study and recent studies of PD-L1 inhibitor monotherapy in the first-line setting in ccRCC¹⁴⁻¹⁶; this may suggest that blocking the interaction of PD-1 with its ligands PD-L1 and PD-L2 may have a therapeutic benefit over blocking only the interaction of PD-L1 with PD-1 in RCC. Given these observations, the role of PD-1 versus PD-L1 blockade, as well as the differences in the first-line versus the second-line activity, merits further evaluation in ccRCC.

In recent years, anti-PD-1 and anti-PD-L1 blocking agents have been evaluated in various combination regimens as first-line treatment for patients with RCC. Results of three pivotal studies showed improved efficacy of the combinations over the single-agent VEGF-TKI (eg, sunitinib) comparators, which led to the FDA approval of nivolumab plus ipilimumab, pembrolizumab plus axitinib, and avelumab plus axitinib for the first-line treatment of patients with advanced RCC.^{2,4} A lower percentage of patients who received pembrolizumab monotherapy in our study experienced treatment-related AEs and discontinued because of treatment-related AEs than was seen with the current FDA-approved combinations.^{2,4}

Although the single-arm nature of this study limits conclusions, the safety data of the current analysis suggest that pembrolizumab monotherapy may be better tolerated than the approved PD-1-based and PD-L1-based combination therapies.^{2,4} Treatment with pembrolizumab monotherapy may therefore be a potential treatment option for those patients who are not able to tolerate an immunotherapy-based combination. The efficacy and safety outcomes of the current analysis provide some insight into the potential contribution of the PD-1 pathway blockade component of various combination regimens. Firm conclusions on how much of the efficacy and safety observed with the combination therapies is attributable to PD-1 or PD-L1 inhibition will require properly designed randomized trials.

Despite the limitations inherent in a single-arm design, the results of this study show that pembrolizumab monotherapy has promising antitumor activity and acceptable safety as a first-line treatment in patients with advanced ccRCC, including patients across all IMDC risk groups and patients with PD-L1-positive and PD-L1-negative tumors. Results presented herein help to place the results of current—and possibly future—pembrolizumab combination therapies for patients with advanced RCC in context. These results also provide support for the exploration of single-agent PD-1 blockade with pembrolizumab in the adjuvant setting (KEYNOTE-564, ClinicalTrials.gov identifier: [NCT03142334](https://clinicaltrials.gov/ct2/show/study/NCT03142334)) and for further exploration of pembrolizumab monotherapy and novel pembrolizumab-based combination regimens in patients in the advanced disease setting.

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Presented in part at the ASCO20 Virtual Meeting, May 29-31, 2020; the 2018 ASCO Annual Meeting (ASCO), Chicago, IL, June 1-5, 2018; the 2018 European Society for Medical Oncology (ESMO) Congress, Munich, Germany, October 19-23, 2018; the 2019 ASCO Annual Meeting (ASCO), Chicago, IL, May 31-June 4, 2019; the 2019 ESMO Annual Meeting, Barcelona, Spain, September 27-October 1, 2019.

SUPPORT

Supported by Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, NJ. This work was also supported by a grant from the National Cancer Institute, USA Kidney SPORE (5P50CA101942).

DATA SHARING STATEMENT

The data sharing policy for Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, NJ, including restrictions, is available at http://engagezone.msd.com/ds_documentation.php. Requests for

access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI <https://doi.org/10.1200/JCO.20.02363>.

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ACKNOWLEDGMENT

The authors thank the patients and their families and all investigators and site personnel. The authors also thank Scot Ebbinghaus, Karla Rodriguez-Lopez, Trevor Newhook, Jialin Xu, Sabrina Wan, Susmita Gupta, Kate Fogarty, Yuying Hwang (employees of Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, NJ), and Sabina Signoretti (Brigham and Women's Hospital, Boston, MA) for their contributions to the study. Medical writing and/or editorial assistance was provided by Robert Steger, PhD, and Matthew Grzywacz, PhD, of ApotheCom (Yardley, PA), and was funded by Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, NJ. Funding for this research was provided by Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, NJ.

REFERENCES

- Motzer RJ, Escudier B, McDermott DF, et al: Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med* 373:1803-1813, 2015
- Motzer RJ, Tannir NM, McDermott DF, et al: Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med* 378:1277-1290, 2018
- Rini BI, Plimack ER, Stus V, et al: Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 380:1116-1127, 2019
- Motzer RJ, Penkov K, Haanen J, et al: Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 380:1103-1115, 2019
- Heng DY, Xie W, Regan MM, et al: External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: A population-based study. *Lancet Oncol* 14:141-148, 2013
- KEYTRUDA® (pembrolizumab) for Injection, for Intravenous Use. Whitehouse Station, NJ, Merck Sharp & Dohme Corp, 2020
- Baxi S, Yang A, Gennarelli RL, et al: Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: Systematic review and meta-analysis. *BMJ* 360:k793, 2018
- Puzanov I, Diab A, Abdallah K, et al: Managing toxicities associated with immune checkpoint inhibitors: Consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer* 5:95, 2017
- Atkins MB, Clark JI, Quinn DI: Immune checkpoint inhibitors in advanced renal cell carcinoma: Experience to date and future directions. *Ann Oncol* 28:1484-1494, 2017
- Rini BI, Motzer RJ, Powles T, et al: Atezolizumab (atezo) + bevacizumab (bev) versus sunitinib (sun) in pts with untreated metastatic renal cell carcinoma (mRCC) and sarcomatoid (sarc) histology: IMmotion151 subgroup analysis. *J Clin Oncol* 37:4512, 2019

11. Choueiri TK, Albiges L, Haanen JBAG, et al: Biomarker analyses from JAVELIN Renal 101: Avelumab + axitinib (A+Ax) versus sunitinib (S) in advanced renal cell carcinoma (aRCC). *J Clin Oncol* 2019 (suppl; abstr 101)
12. Flippot R, McGregor BA, Flaifel A, et al: Atezolizumab plus bevacizumab in non-clear cell renal cell carcinoma (NccRCC) and clear cell renal cell carcinoma with sarcomatoid differentiation (ccRCCsd): Updated results of activity and predictive biomarkers from a phase II study. *J Clin Oncol* 2019 (suppl; abstr 4583)
13. Lim SH, Sun JM, Lee SH, et al: Pembrolizumab for the treatment of non-small cell lung cancer. *Expert Opin Biol Ther* 16:397-406, 2016
14. McDermott DF, Huseni MA, Atkins MB, et al: Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma. *Nat Med* 24:749-757, 2018
15. Atkins MB, Jegede O, Haas NB, et al: Phase II study of nivolumab and salvage nivolumab + ipilimumab in treatment-naïve patients (pts) with advanced renal cell carcinoma (RCC) (HCRN GU16-260). *J Clin Oncol* 2020 (suppl; abstr 5006)
16. Vaishampayan U, Schoffski P, Ravaud A, et al: First-line or second-line avelumab monotherapy in patients with advanced renal cell carcinoma enrolled in the phase 1b JAVELIN Solid Tumor trial. Presented at the ESMO 2018, Munich, Germany, October 19-23, 2018



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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Open-Label, Single-Arm Phase II Study of Pembrolizumab Monotherapy as First-Line Therapy in Patients With Advanced Clear Cell Renal Cell Carcinoma**

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Research Funding: Bristol-Myers Squibb

No other potential conflicts of interest were reported.

APPENDIX

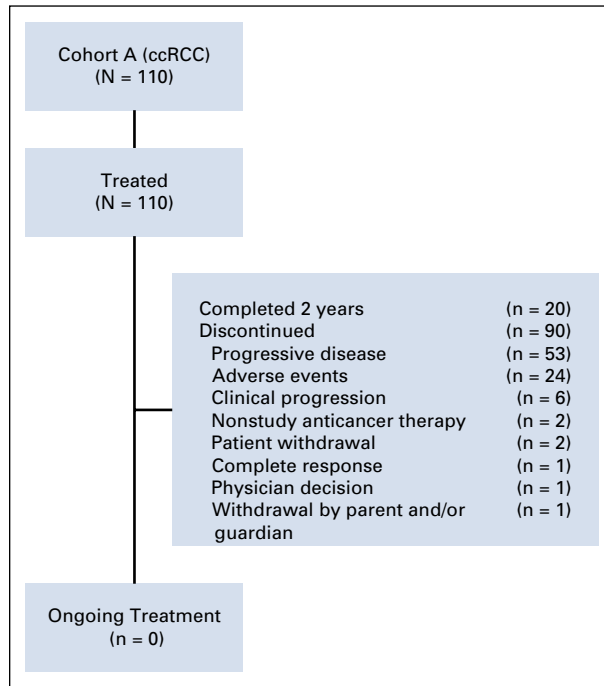


FIG A1. Patient disposition. ccRCC, clear cell renal cell carcinoma.

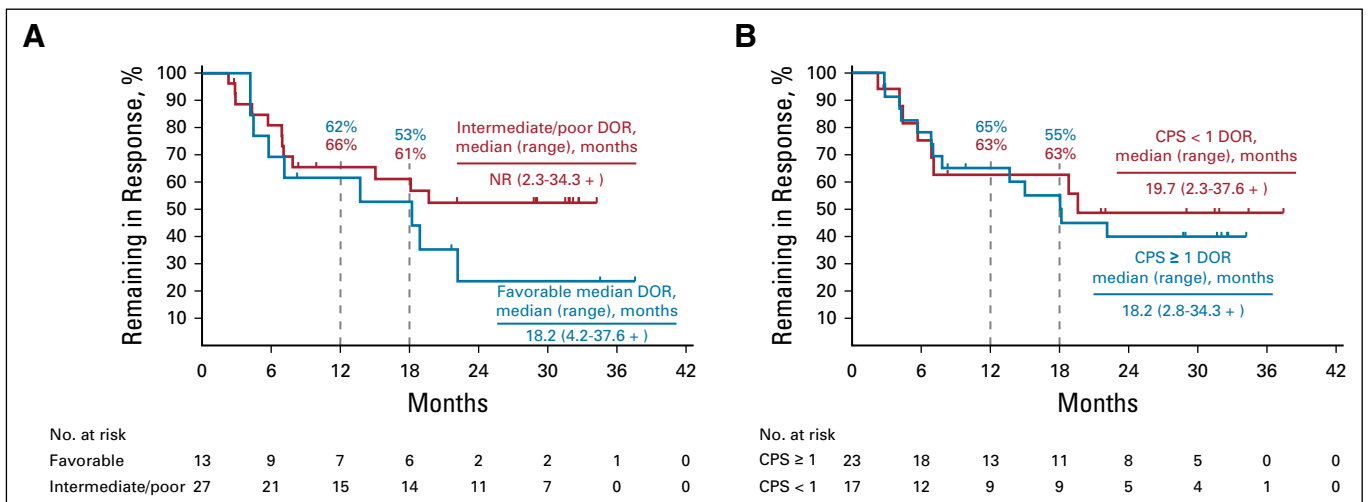


FIG A2. Kaplan-Meier estimates of duration of response by (A) IMDC risk category, and (B) by PD-L1 status. CPS, combined positive score; DOR, duration of response; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; NR, not reached; PD-L1, programmed death ligand 1.