original reports

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

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abstract

PURPOSE Programmed death 1 (PD-1) pathway inhibitors have not been prospectively evaluated in patients with non–clear cell renal cell carcinoma (nccRCC). The phase II KEYNOTE-427 study (cohort B) was conducted to assess the efficacy and safety of single-agent pembrolizumab, a PD-1 inhibitor, in advanced nccRCC.

METHODS Patients with histologically confirmed, measurable (Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) nccRCC and no prior systemic therapy received pembrolizumab 200 mg intravenously once every 3 weeks for ≤ 24 months. The primary end point was objective response rate (ORR) per RECIST v1.1.

RESULTS Among enrolled patients (N = 165), 71.5% had confirmed papillary, 12.7% had chromophobe, and 15.8% had unclassified RCC histology. Most patients (67.9%) had intermediate or poor International Metastatic RCC Database Consortium risk status and tumors with programmed death ligand 1 (PD-L1) combined positive score (CPS) ≥ 1 (61.8%). The median time from enrollment to database cutoff was 31.5 months (range, 22.7-38.8). In all patients, the ORR was 26.7%. The median duration of response was 29.0 months; 59.7% of responses lasted ≥ 12 months. The ORR by CPS ≥ 1 and CPS < 1 status was 35.3% and 12.1%, respectively. The ORR by histology was 28.8% for papillary, 9.5% for chromophobe, and 30.8% for unclassified. Overall, the median progression-free survival was 4.2 months (95% CI, 2.9 to 5.6); the 24-month rate was 18.6%. The median overall survival was 28.9 months (95% CI, 24.3 months to not reached); the 24-month rate was 58.4%. Overall, 69.7% of patients reported treatment-related adverse events, most commonly pruritus (20.0%) and hypothyroidism (14.5%). Two deaths were treatment related (pneumonitis and cardiac arrest).

CONCLUSION First-line pembrolizumab monotherapy showed promising antitumor activity in nccRCC. The safety profile was similar to that observed in other tumor types.

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ASSOCIATED CONTENT

Data Supplement
Protocol

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

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INTRODUCTION

Worldwide, it is estimated that more than 400,000 people will be diagnosed with kidney cancer in 2020.[1] Because the most common type of kidney cancer is renal cell carcinoma (RCC) and approximately 70% of patients with RCC have clear cell histology (ccRCC), most approved therapies were developed in the ccRCC population.[2] The remaining cases of RCC, broadly defined as non–clear cell renal cell carcinoma (nccRCC), compose a heterogeneous group of tumors that originate from the kidney and lack effective therapies.[3] Most clinical trials in patients with nccRCC have been conducted to explore antivascular endothelial growth factor (VEGF) therapies in predominantly papillary RCC populations, and objective response rates (ORR) were low (< 15%).[2,3] The data for mammalian target of rapamycin (mTOR) inhibitors suggest even lower overall efficacy in patients with nccRCC.[3] Because of the limited positive clinical trial data for antiangiogenic and mTOR-targeted agents in patients with nccRCC, the National Comprehensive Cancer Network (NCCN) treatment guidelines recommend participation in a clinical trial as a preferred strategy for patients with nccRCC.[2]

Cytokine-based immunotherapies such as interleukin 2 and interferon α were beneficial in only a small group of patients with RCC and showed virtually no activity in patients with nccRCC.[4-7] As understanding of the role

CONTEXT

Key Objective

To determine if it is possible to treat advanced or metastatic non–clear cell renal cell carcinoma (nccRCC) with pembrolizumab monotherapy in the first-line setting.

Knowledge Generated

Pembrolizumab monotherapy demonstrated promising antitumor activity and survival in patients treated in the first-line setting of advanced or metastatic nccRCC. Pembrolizumab monotherapy demonstrated an objective response rate of 26.7% in the overall nccRCC population, which was consistent across key subgroups including International Metastatic RCC Database risk groups, patients with varying histologic subtypes, and patients with tumors with high-programmed death ligand 1 status. The median progression-free survival was 4.2 months, and the median overall survival was 28.9 months.

Relevance

Pembrolizumab monotherapy may be a potential treatment option for nccRCC.

of immune evasion in RCC has improved, more recent treatment approaches for patients with advanced RCC have used immune checkpoint inhibitors that target the programmed death 1 (PD-1) and the cytotoxic T-lymphocyte–associated antigen (CTLA-4) pathways. Therefore, it was likely that there was therapeutic potential in inhibiting the PD-1 pathway in patients with nccRCC. The phase II KEYNOTE-427 study (ClinicalTrials.gov identifier: NCT02853344) was conducted to evaluate the efficacy and safety of the PD-1 inhibitor pembrolizumab as monotherapy for first-line treatment of patients with advanced ccRCC (cohort A) and patients with advanced nccRCC (cohort B). Analysis of cohort A showed that pembrolizumab monotherapy has considerable antitumor activity in previously untreated patients with ccRCC.[8] Herein, we present the results of pembrolizumab monotherapy in previously untreated patients with nccRCC (cohort B).

METHODS

Study Design and Objectives

KEYNOTE-427 (ClinicalTrials.gov identifier: NCT02853344) was an international, single-arm, open-label, multicohort, multicenter phase II trial performed at 61 sites in 10 countries. Patients enrolled in the study were administered intravenous pembrolizumab 200 mg once every 3 weeks until disease progression, unacceptable toxicity, or a total treatment duration of 24 months (maximum of 35 doses). The primary objective was to estimate ORR per RECIST, version 1.1 (RECIST v1.1) as assessed by blinded independent central review (BICR) in patients with nccRCC.

The Protocol and its amendments were approved by the appropriate institutional review board or independent ethics committee at each site. The trial was conducted per Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent.

Patient Characteristics

Eligible patients were ≥ 18 years with newly diagnosed or recurrent stage IV nccRCC as determined by the investigator and measurable disease per RECIST v1.1. Diagnosis of nccRCC was retrospectively confirmed by central pathology review. Subtype histology of nccRCC was determined by central pathology review. Patients must not have received prior systemic therapy for metastatic disease and must have maintained a Karnofsky performance status score ≥ 70 within 10 days before initiating treatment. Prior neoadjuvant and/or adjuvant therapy for RCC was allowed if it was completed more than 12 months before allocation and if it did not include a PD-1 pathway blocker. Exclusion criteria are provided in the Data Supplement (online only).

Study Assessments

The primary end point was ORR, per RECIST v1.1 as assessed by BICR. Secondary end points were duration of response (DOR), disease control rate (DCR; defined as the sum of complete responders, partial responders, and patients with stable disease lasting ≥ 6 months), progression-free survival (PFS; defined as the time from first day of study treatment to first documented disease progression per RECIST v1.1 or death, whichever occurred first), overall survival (OS; defined as the time from first day of study treatment to time of death) per RECIST v1.1 by BICR, and safety and tolerability. Exploratory end points were ORR, DOR, and DCR in relation to (1) histology, (2) International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk status, (3) programmed death ligand 1 (PD-L1) combined positive score (CPS), and (4) sarcomatoid differentiation.

Tumor imaging was performed using computed tomography or magnetic resonance imaging of the chest, abdomen, or pelvis. Imaging assessments were performed at week 12, then every 6 weeks until week 54, and every 12 weeks thereafter. Baseline bone imaging was necessary for confirmation of complete response (CR) and was

performed at screening and at weeks 18, 30, 42, and 54, and then every 24 weeks thereafter. Response was assessed according to RECIST v1.1 based on BICR.

Assessment of PD-L1 expression and sarcomatoid differentiation is described in the Data Supplement.

Safety was monitored throughout the study and for 30 days after the last dose of pembrolizumab and graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4. Any adverse events (AEs) associated with pembrolizumab exposure with immunologic etiology were recorded as immune-mediated AEs. Patients were monitored for any serious AEs and immune-mediated AEs for up to 90 days after study completion.

Statistical Analyses

ORR was calculated as the proportion of patients in the analysis population who experienced CR or partial response (PR). The 95% CIs were calculated using the Clopper-Pearson method based on binomial distribution. 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. The DOR analysis population included all responders. No statistical adjustments were performed for multiple comparisons.

RESULTS

Patients

In total, 165 patients were enrolled across nine countries in cohort B. The median time from enrollment to database cutoff was 31.5 months (range, 22.7-38.8). The median age was 62 years (range, 22-86), and 66.1% of patients were male (Table 1). The median duration of therapy was 6.9 months (range, 0.03-29.2). The PD-L1 expression status was CPS ≥ 1 in 61.8% (n = 102) of patients. Fifty-three patients (32.1%) and 112 patients (67.9%) were classified into favorable and intermediate or poor IMDC risk categories, respectively.

At data cutoff on February 24, 2020, treatment was ongoing in two patients (1.2%), had been discontinued in 139 patients (84.2%), and was completed in 24 patients (14.5%). Most patients (66.1%) discontinued treatment because of progressive disease (57.0%) or clinical progression (9.1%). Treatment was discontinued because of an AE in 25 patients (15.2%); 16 patients (9.7%) discontinued treatment because of a treatment-related AE (Data Supplement Figure S1, online only). Other reasons for discontinuation were patient withdrawal (n = 3) and treatment with other anticancer therapy (n = 1).

Efficacy Outcomes in the Total Population

The ORR was 26.7% (95% CI, 20.1 to 34.1) in the total population: 11 patients (6.7%) achieved CR and 33 patients (20.0%) achieved PR; the DCR was 43.0% (Table 2). Ninety-one patients (55.2%) had a reduction in target lesions; 20 patients (12.1%) had reductions ≥ 80%, and seven patients (4.2%) had 100% target lesion reduction (Fig 1A).

TABLE 1. Patient Demographics and Characteristics at Baseline

Characteristic	Pembrolizumab (N = 165)
Sex	
Male	109 (66.1)
Female	56 (33.9)
Age, years	
Median (range)	62 (22-86)
≥ 65	59 (35.8)
Geographic region	
North America	42 (25.5)
Western Europe	46 (27.9)
Rest of world	77 (46.7)
KPS score	
90-100	124 (75.2)
70-80	41 (24.8)
IMDC risk category	
Favorable	53 (32.1)
Intermediate or poor	112 (67.9)
PD-L1 CPS	
≥ 1	102 (61.8)
< 1	58 (35.2)
Missing data	5 (3.0)
RCC histology	
Papillary	118 (71.5)
Chromophobe	21 (12.7)
Unclassified	26 (15.8)
Site of metastatic disease	
Lungs	72 (43.6)
Lymph node	91 (55.2)
Bone	49 (29.7)
Liver	46 (27.9)
Adrenal gland	23 (13.9)
Sarcomatoid feature	
Yes	38 (23.0)
No	93 (56.4)
Unknown	34 (20.6)
Prior oncologic radiation	19 (11.5)
Prior nephrectomy	127 (77.0)

NOTE. All values are represented as n (%) unless otherwise specified.
Abbreviations: CPS, combined positive score; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; KPS, Karnofsky Performance Status; PD-L1, programmed death ligand 1; RCC, renal cell carcinoma.

The median time to response was 2.8 months (range, 0.1-8.3), and the median DOR was 29.0 months (range, 2.8-31.6 +). By Kaplan-Meier estimate, the percentage of responders with response durations ≥ 12 months and

≥ 18 months was 59.7% and 57.0%, respectively (Fig 1B). Of the 44 patients who experienced a CR or PR, 19 had an ongoing response at data cutoff (Fig 1B) and 20 had experienced subsequent progressive disease per BICR (Fig 1C). For the other five responders, two discontinued treatment because of an AE (acute coronary syndrome and hemorrhagic stroke), two because of radiographic progression, and one because of clinical progression.

The median PFS for the entire nccRCC group was 4.2 months (95% CI, 2.9 to 5.6) (Fig 2A); 12- and 24-month PFS rates were 24.7% and 18.6%, respectively. The 12- and 24-month OS rates were 73.2% and 58.4%, respectively; the median OS was 28.9 months (95% CI, 24.3 months to not reached; Fig 2B).

Efficacy Outcomes by PD-L1 Expression

For patients with CPS ≥ 1 (n = 102), the confirmed ORR was 35.3% (95% CI, 26.1 to 45.4) (Fig 3; Table 2). The DCR was 50.0% (95% CI, 39.9 to 60.1). The median DOR was 29.0 months (range, 2.8 + to 31.6 +), the median PFS was 5.6 months (95% CI, 2.9 to 8.3), and the median OS was 30.0 months (95% CI, 22.9 to not reached) (Data Supplement Table S1, online only). For patients with CPS < 1 (n = 58), the confirmed ORR was 12.1% (95% CI, 5.0 to 23.3) (Fig 3; Table 2). The DCR was 31.0% (95% CI, 19.5 to 44.5). The median DOR was 9.5 months (range, 2.8 to 26.0 +), the median PFS was 3.7 months (95% CI, 2.8 to 4.2), and the median OS was 26.6 months (95% CI, 19.2 months to not reached) (Data Supplement Table S1).

Efficacy Outcomes by Histology

The confirmed ORRs for patients with papillary, chromophobe, and unclassified histology were 28.8% (95% CI, 20.8% to 37.9%), 9.5% (95% CI, 1.2% to 30.4%), and 30.8% (95% CI, 14.3% to 51.8%), respectively (Fig 3; Table 2). The median DOR ranged from 29.0 months to not reached (Data Supplement Table S1). For patients with papillary histology, the DCR was 47.5% (95% CI, 38.2% to 56.9%), the median PFS was 5.5 months (95% CI, 3.9 to 6.9), and the median OS was 31.5 (95% CI, 25.5 to not reached) (Table 2; Data Supplement Table S1). For patients with chromophobe histology, the DCR was 33.3% (95% CI, 14.6% to 57.0%), the median PFS was 3.9 months (95% CI, 2.6 to 6.9), and the median OS was 23.5 months (95% CI, 9.3 to not reached) (Table 2, Data Supplement Table S1). For patients with unclassified histology, the DCR was 30.8% (95% CI, 14.3% to 51.8), the median PFS was 2.8 months (95% CI, 2.8 to 5.1), and the median OS was 17.6 months (95% CI, 7.5 to not reached) (Data Supplement Table S1).

Efficacy by Sarcomatoid Differentiation

Among patients with sarcomatoid differentiation (n = 38), the confirmed ORR was 42.1% (95% CI, 26.3% to 59.2%) (Fig 3; Table 2). The DCR was 55.3% (95% CI, 38.3% to 71.4%) (Table 2). The median DOR was 15.3 months (range, 2.8 + to 29.5 +), the median PFS was 6.9 months (95% CI, 2.8 to 15.4), and the median OS was 25.5 months (95% CI, 13.1 to 30.0) (Data Supplement Table S1).

Efficacy Outcomes by IMDC Risk Category

For patients with favorable IMDC risk (n = 53), the confirmed ORR was 32.1% (95% CI, 19.9% to 46.3%) (Fig 3; Table 2). The DCR was 43.4% (95% CI, 29.8% to 57.7%). The median DOR was 11.0 months (range, 2.8 to 27.7 +), the median PFS was 5.3 months (95% CI, 2.9 to 8.2), and the median OS was not reached (95% CI, 30.4 to not reached) (Data Supplement Table S1).

In the intermediate or poor IMDC risk subgroup (n = 112), the confirmed ORR was 24.1% (95% CI, 16.5% to 33.1%) (Fig 3; Table 2). The DCR was 42.9% (95% CI, 33.5% to 52.6%). The median DOR was 29.0 months (range, 2.8 to 31.6 +), the median PFS was 4.0 months (95% CI, 2.8 to 6.2), and the median OS was 24.5 months (95% CI, 16.7 to 30.0) (Data Supplement Table S1).

Safety

A total of 69.7% of patients experienced treatment-related AEs of any grade; 17% experienced treatment-related AEs of grade 3-5 (Table 3). The most commonly reported treatment-related AEs of any grade were pruritus (20.0%), hypothyroidism (14.5%), fatigue (13.9%), and diarrhea (13.9%). Colitis (1.8%) and fatigue (1.8%) was the most commonly reported grade 3-5 treatment-related AE. Discontinuation because of a treatment-related AE was reported for 16 patients (9.7%) (Data Supplement Table S2, online only). Eight patients died of AEs, two of which were considered related to treatment (pneumonia and cardiac arrest); six deaths (pneumonia, ischemic stroke, respiratory failure, bleeding from esophageal varices left ventricular failure, and multiple organ dysfunction syndrome) were not considered related to treatment. Immune-mediated AEs were reported in 32.7% of patients (grade 1 or 2, 40 of 54 patients) (Table 3). The most commonly reported immune-mediated AEs were hypothyroidism (15.8%), hyperthyroidism (6.7%), colitis (2.4%), and hepatitis (2.4%). Hepatitis (2.4%) was the most commonly reported grade 3-5 immune-mediated AE.

Systemic corticosteroids were used for the management of 71 immune-related AE episodes. Eighteen episodes (25.4%) were managed with a high starting dose of corticosteroids (≥ 40 mg/d prednisone or equivalent), and four (5.6%) were managed with a low starting dose of corticosteroids (< 40 mg/d prednisone or equivalent). The remaining 49 episodes (69.0%) did not necessitate treatment with corticosteroids.

DISCUSSION

The single-arm, phase II KEYNOTE-427 study is the first and largest interventional clinical study conducted in a cohort of patients with previously untreated advanced

TABLE 2. Response Rate in the Overall Population and in Patient Subgroups Per RECIST v1.1 by BICR

Parameter	Overall (N = 165)	RCC Histology			IMDC Category		PD-L1 Status n = 160		Sarcomatoid Differentiation (n = 38)
		Papillary (n = 118)	Chromophobe (n = 21)	Unclassified (n = 26)	Favorable (n = 53)	Intermediate or Poor (n = 112)	CPS < 1 (n = 58)	CPS ≥ 1 (n = 102)	
ORR, % (95% CI)	26.7 (20.1 to 34.1)	28.8 (20.8 to 37.9)	9.5 (1.2 to 30.4)	30.8 (14.3 to 51.8)	32.1 (19.9 to 46.3)	24.1 (16.5 to 33.1)	12.1 (5.0 to 23.3)	35.3 (26.1 to 45.4)	42.1 (26.3 to 59.2)
DCR (CR + PR + SD ≥ 6 mo), (95% CI)	43.0 (35.4 to 51.0)	47.5 (38.2 to 56.9)	33.3 (14.6 to 57.0)	30.8 (14.3 to 51.8)	43.4 (29.8 to 57.7)	42.9 (33.5 to 52.6)	31.0 (19.5 to 44.5)	50.0 (39.9 to 60.1)	55.3 (38.3 to 71.4)
Best response, n (%)									
CR	11 (6.7)	7 (5.9)	1 (4.8)	3 (11.5)	7 (13.2)	4 (3.6)	3 (5.2)	8 (7.8)	4 (10.5)
PR	33 (20.0)	27 (22.9)	1 (4.8)	5 (19.2)	10 (18.9)	23 (20.5)	4 (6.9)	28 (27.5)	12 (31.6)
SD	51 (30.9)	39 (33.1)	10 (47.6)	2 (7.7)	17 (32.1)	34 (30.4)	24 (41.4)	25 (24.5)	7 (18.4)
PD	60 (36.4)	38 (32.2)	9 (42.9)	13 (50.0)	18 (34.0)	42 (37.5)	24 (41.4)	34 (33.3)	12 (31.6)
Nonevaluable[a]	2 (1.2)	1 (0.8)	0 (0)	1 (3.8)	1 (1.9)	1 (0.9)	0 (0)	2 (2.0)	1 (2.6)
No assessment[b]	8 (4.8)	6 (5.1)	0 (0)	2 (7.7)	0 (0)	8 (7.1)	3 (5.2)	5 (4.9)	2 (5.3)

Abbreviations: BICR, blinded independent central review; CPS, combined positive score, CR, complete response; DCR, disease control rate; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death ligand 1; PR, partial response; RCC, renal cell carcinoma; SD, stable disease.

[a]Includes patients with insufficient data for assessment of response.

[b]Includes patients who discontinued treatment or died before the first baseline imaging.

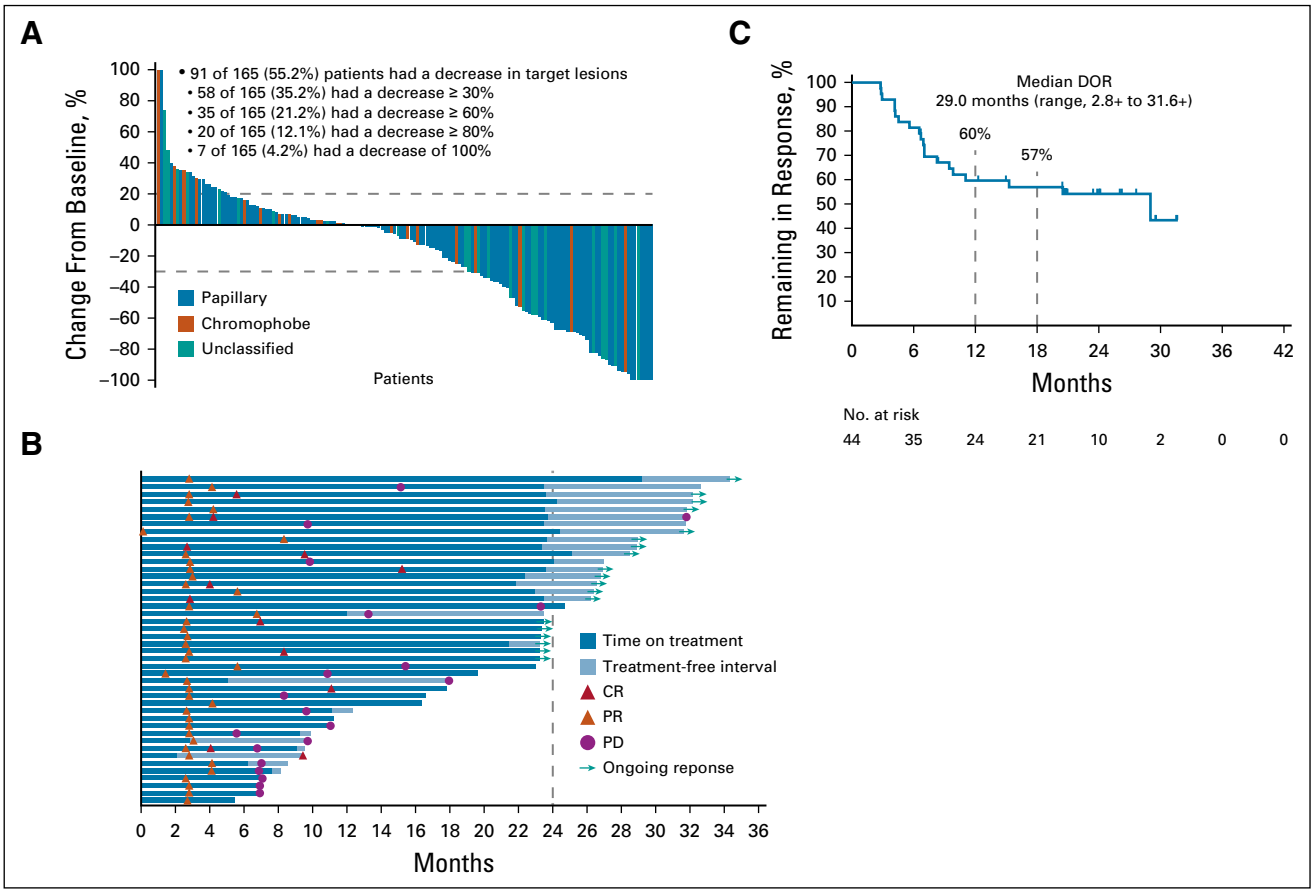

FIG 1. Maximum change from baseline in target lesions (A),[a] time to response and response duration (B), and Kaplan-Meier estimate of DOR (C) based on blinded independent central review. [a]Maximum change from baseline in target lesions by central review was assessed for patients who received ≥ 1 dose of pembrolizumab, had baseline imaging with measurable disease per RECIST v1.1, and had a postbaseline assessment (n = 155). +, ongoing response; CR, complete response; DOR, duration of response; PD, progressive disease; PR, partial response.

nccRCC. First-line pembrolizumab monotherapy showed promising antitumor activity (ORR = 26.7%) in the overall nccRCC population, consistent results across IMDC risk groups, and promising activity in selected patient subgroups with tumors with high PD-L1 expression, papillary or unclassified histology, and sarcomatoid differentiation. The

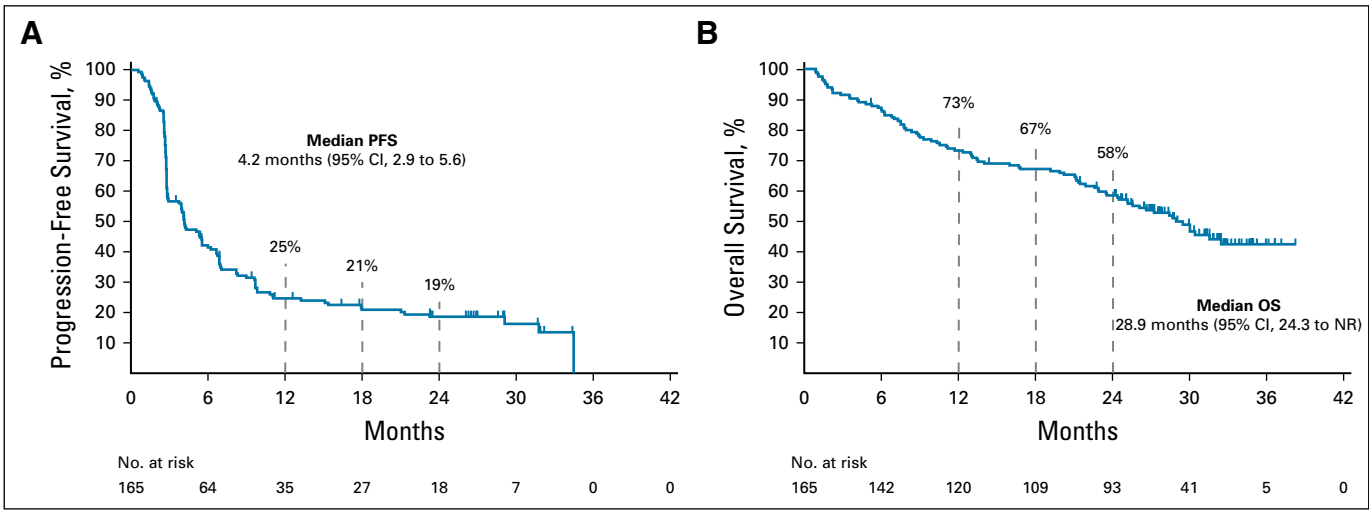

FIG 2. Kaplan-Meier curves for (A) progression-free survival and (B) overall survival. NR, not reached; OS, overall survival; PFS, progression-free survival.

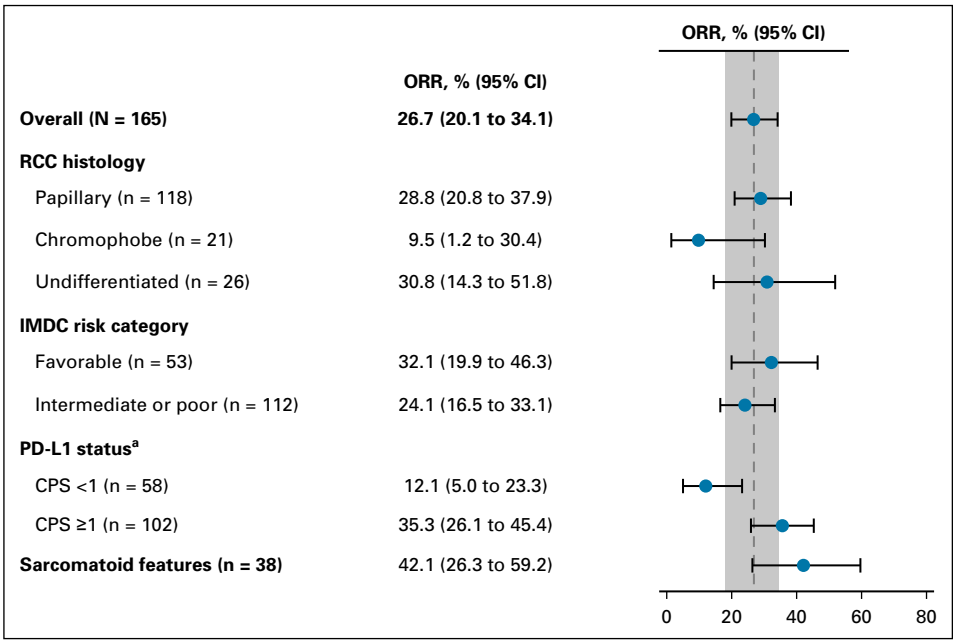

FIG 3. ORR by patient subgroup. [a]Five patients had missing PD-L1 status. CPS, combined positive score; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; ORR, objective response rate; PD-L1, programmed death ligand 1; RCC, renal cell carcinoma.

median DOR was 29.0 months, with most patients achieving a response for ≥ 12 months. The median PFS was 4.2 months, the median OS was 28.9 months, and the 24-month OS rate was 58.4%. These findings are consistent with those of other studies of PD-1/PD-L1 inhibitors, both as monotherapy and in combination treatment.[9-12]

The results of the current study show that pembrolizumab monotherapy provides durable antitumor activity in untreated patients with nccRCC. Furthermore, the confirmation of an nccRCC diagnosis by central pathology in KEYNOTE-427 provides confidence in our results, given the histologic diversity of these cancers.

Because the focus of RCC clinical trials of targeted systemic therapies has predominantly been on patients with ccRCC, the NCCN kidney cancer guidelines indicate that enrollment in clinical trials is the preferred strategy for patients with nccRCC.[2] Current standard-of-care systemic treatment options recommended by NCCN guidelines for patients with nccRCC include sunitinib, everolimus, and cabozantinib.[2] The phase II ASPEN and ESPN trials were conducted to assess efficacy and safety of sunitinib versus everolimus in patients with nccRCC, and recommendations were primarily based on the results of the primary end point of PFS.[13,14] Notably, nccRCC histology in ASPEN and ESPN was not confirmed by central pathology review. Tumor response was evaluated as a secondary end point in both trials. In the ASPEN trial, the ORR was 18% (PR, n = 9) in the sunitinib arm and 9% (CR, n = 2; PR, n = 4) in the everolimus arm.[13] In the ESPN trial, the ORR was 9% (PR, n = 3) with first-line sunitinib and 3% (PR, n = 1) with first-line everolimus.[14] Despite guideline recommendations for these regimens, the results of these approaches demonstrate that more effective treatment options for nccRCC are needed.

The safety profile of pembrolizumab monotherapy in this study is generally consistent with what has been observed in other tumor types.[15] Overall, 69.7% of patients reported treatment-related AEs of any grade and 17% reported treatment-related AEs of grade 3-5. The most reported immune-mediated AEs were hypothyroidism, hyperthyroidism, colitis, and hepatitis, consistent with a recent systematic review and meta-analysis of PD-1/PD-L1 inhibitors.[16] Two of the eight deaths that occurred in the study were considered related to treatment (pneumonitis and cardiac arrest). Although rare, serious and potentially fatal cases of pneumonitis and cardiotoxicity can occur with the use of immune checkpoint inhibitors such as pembrolizumab.[17,18]

The antitumor activity of pembrolizumab monotherapy was also demonstrated across key patient subgroups. ORR in the overall nccRCC population was similar to ORRs in the favorable and intermediate or poor IMDC risk groups, suggesting that antitumor activity was generally consistent across IMDC risk categories. When evaluated by RCC histology, ORRs were higher for patients with papillary and unclassified RCC than for patients with chromophobe RCC. This result is similar to that reported in a retrospective analysis of nivolumab in nccRCC, in which the highest response rate was observed in patients with unclassified histology, followed by papillary and

TABLE 3. Treatment-Related and Immune-Mediated AEs

AE (N = 165)	Any Grade (≥ 2 patients)	Grades 3-5
AEs		
Any	115 (69.7)	28 (17.0)
Pruritis	33 (20.0)	0 (0)
Hypothyroidism	24 (14.5)	0 (0)
Fatigue	23 (13.9)	3 (1.8)
Diarrhea	23 (13.9)	0 (0)
Rash	16 (9.7)	0 (0)
Asthenia	10 (6.1)	0 (0)
Arthralgia	10 (6.1)	0 (0)
Dry mouth	10 (6.1)	0 (0)
Hyperthyroidism	10 (6.1)	0 (0)
Decreased appetite	9 (5.5)	0 (0)
Nausea	9 (5.5)	0 (0)
Vomiting	9 (5.5)	0 (0)
Increased AST	8 (4.8)	1 (0.6)
Myalgia	8 (4.8)	0 (0)
Dry skin	7 (4.2)	0 (0)
Increased ALT	7 (4.2)	1 (0.6)
Maculopapular rash	7 (4.2)	1 (0.6)
Influenza-like illness	5 (3.0)	0 (0)
Anemia	4 (2.4)	1 (0.6)
Colitis	4 (2.4)	3 (1.8)
Decreased weight	4 (2.4)	0 (0)
Headache	4 (2.4)	0 (0)
Lethargy	4 (2.4)	0 (0)
Pyrexia	4 (2.4)	0 (0)
Alopecia	3 (1.8)	0 (0)
Arthritis	3 (1.8)	0 (0)
Chills	3 (1.8)	0 (0)
Decreased neutrophil count	3 (1.8)	0 (0)
Increased blood creatinine	3 (1.8)	1 (0.6)
Musculoskeletal pain	3 (1.8)	0 (0)
Nephritis	3 (1.8)	1 (0.6)
Pneumonitis	3 (1.8)	0 (0)
Abdominal discomfort	2 (1.2)	0 (0)
Adrenal insufficiency	2 (1.2)	1 (0.6)
Autoimmune hepatitis	2 (1.2)	2 (1.2)
Cough	2 (1.2)	0 (0)
Decreased lymphocyte count	2 (1.2)	0 (0)
Dyspnea	2 (1.2)	1 (0.6)
Gastritis	2 (1.2)	0 (0)
Hepatitis	2 (1.2)	2 (1.2)
Hyperuricemia	2 (1.2)	0 (0)

(continued on following page)

TABLE 3. Treatment-Related and Immune-Mediated AEs (continued)

AE (N = 165)	Any Grade (≥ 2 patients)	Grades 3-5
Hypokalemia	2 (1.2)	1 (0.6)
Increased blood alkaline phosphatase	2 (1.2)	1 (0.6)
Lipase increased	2 (1.2)	2 (1.2)
Mucosal inflammation	2 (1.2)	0 (0)
Myocarditis	2 (1.2)	2 (1.2)
Myositis	2 (1.2)	1 (0.6)
Neutropenia	2 (1.2)	0 (0)
Palmar-plantar erythrodysaesthesia syndrome	2 (1.2)	0 (0)
Peripheral edema	2 (1.2)	0 (0)
Polyarthritis	2 (1.2)	2 (1.2)
Stomatitis	2 (1.2)	1 (0.6)
Type 1 diabetes mellitus	2 (1.2)	2 (1.2)
Immune-mediated AE[a]		
Any	54 (32.7)	14 (8.5)
Hypothyroidism	26 (15.8)	0 (0)
Hyperthyroidism	11 (6.7)	0 (0)
Colitis	4 (2.4)	3 (1.8)
Hepatitis	4 (2.4)	4 (2.4)
Nephritis	3 (1.8)	1 (0.6)
Pneumonitis	3 (1.8)	0 (0)
Adrenal insufficiency	2 (1.2)	1 (0.6)
Myocarditis	2 (1.2)	2 (1.2)
Myositis	2 (1.2)	1 (0.6)
Type 1 diabetes mellitus	2 (1.2)	2 (1.2)
Thyroiditis	2 (1.2)	0 (0)

NOTE. All values are No. (%) unless otherwise specified.

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

[a]Based on a list of terms specified by the sponsor and included regardless of attribution by the investigator to study treatment or immune relatedness; related terms are included.

chromophobe RCC.[10] Although there were few patients in this study with chromophobe RCC (n = 21) to draw meaningful conclusions, it is unclear why these patients seem to have a poorer response with anti-PD-1 therapies because this histologic subtype is traditionally associated with better survival than other RCC subtypes.[19] Given the rarity of chromophobe histology, the majority of studies are retrospective with substantial heterogeneity; therefore, there is no consensus on the optimal therapy for patients with chromophobe histology.[20] The effectiveness of pembrolizumab might also be influenced by PD-L1 status. Despite differing methodologies (eg, choice of antibody) and positivity thresholds (eg, ≥ 5% positivity), PD-L1 expression has been reported in 11%-20% of samples from patients with nccRCC.[21-25] Following the same methodology as used in this study, PD-L1 expression, defined as CPS ≥ 1, in the KEYNOTE-426 and KEYNOTE-427 cohort A studies was reported in 47% and 60% of patients with ccRCC, respectively.[8,26] Although responses in this study were observed in patients with CPS ≥ 1 and those with CPS < 1, the ORR was three times higher in patients with CPS ≥ 1 (35.3%) than in those with CPS < 1 (12.1%). The results of this study also showed relatively high response rates in patients with sarcomatoid differentiation (ORR, 42.1%). Recently reported results of ongoing studies suggest that sarcomatoid differentiation and DNA and RNA analyses of the tumor microenvironment may play a role in predicting response to PD-1 or PD-L1 inhibitors.[11,27,28] Data from the current study suggest that sarcomatoid differentiation may be a histologic biomarker for response to checkpoint inhibitor therapy in patients with nccRCC, as was observed in patients with ccRCC.

The current study has several limitations. First, the single-arm study design limits comparisons of response rate and survival outcomes with currently recommended regimens. Second, the heterogeneity of the nccRCC patient

population makes subgroup analyses difficult to identify which patients achieve the greatest benefit. Furthermore, despite central pathology review, we were unable to subgroup patients into papillary type I and type II.

In conclusion, pembrolizumab monotherapy showed promising antitumor activity and survival for patients with nccRCC. The safety and tolerability of pembrolizumab monotherapy are consistent with those reported in previous studies. Given the lack of established therapy for nccRCC and favorable ORR relative to VEGF and mTOR therapies, pembrolizumab monotherapy may be a potential treatment option for nccRCC. Additional studies to evaluate antitumor activity of immune checkpoint blockade coupled with studies to validate tissue-based biomarkers of response will better elucidate the role of pembrolizumab treatment in nccRCC.

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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.

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

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