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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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.

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...
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 mono-
therapy in previously untreated patients with nccRCC.

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 du-
arion 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 investiga-
tor and measurable disease per RECIST v1.1. Diagnosis
of nccRCC was retrospectively confirmed by central path-
ology review. Subtype histology of nccRCC was deter-
mined 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 Meta-
static 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 (86.1%) 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)               |
| **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**           |                         |
| 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
Ef 19.2 months to not reached) (Data Supplement Table S1).

2.8 to 4.2), and the median OS was 26.6 months (95% CI, 2.8 to 26.0
CPS (Data Supplement Table S1, online only). For patients with
OS was 30.0 months (95% CI, 22.9 to not reached)
was 5.6 months (95% CI, 2.9 to 8.3), and the median
5.0 to 23.3) (Fig 3; Table 2). The DCR was 31.0% (95% CI, 14.3% to 51.8%),
For patients with CPS
was 5.6 months (95% CI, 2.8 to 36.0 +), 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 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, chromophone, 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 chromophone 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 |
|----------------------------------|-------------------|---------------|---------------|--------------|
|                                  |                   | 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) | Sarcomatoid Differentiation (n = 38) |
| 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 | PR | SD | PD | Nonevaluable<sup>a</sup> | No assessment<sup>b</sup> |
|----------------------|----|----|----|----|--------------------------|------------------------|
| ORR                  | 11 (6.7) | 33 (20.0) | 51 (30.9) | 60 (36.4) | 2 (1.2) | 8 (4.8) |
| DCR                  | 7 (5.9) | 27 (22.9) | 39 (33.1) | 38 (32.2) | 1 (0.8) | 6 (5.1) |
| CR                   | 1 (4.8) | 1 (4.8) | 10 (47.6) | 9 (42.9) | 0 (0) | 0 (0) |
| PR                   | 3 (11.5) | 5 (19.2) | 2 (7.7) | 13 (50.0) | 1 (3.8) | 2 (7.7) |
| SD                   | 7 (13.2) | 10 (18.9) | 17 (32.1) | 18 (34.0) | 1 (1.9) | 0 (0) |
| PD                   | 4 (3.6) | 23 (20.5) | 34 (30.4) | 42 (37.5) | 1 (0.9) | 8 (7.1) |
| Nonevaluable<sup>a</sup> | 3 (5.2) | 4 (6.9) | 24 (41.4) | 24 (41.4) | 0 (0) | 3 (5.2) |
| No assessment<sup>b</sup> | 8 (7.8) | 28 (27.5) | 25 (24.5) | 34 (33.3) | 2 (2.0) | 5 (4.9) |
| 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. |
|<sup>a</sup>Includes patients with insufficient data for assessment of response. |
|<sup>b</sup>Includes patients who discontinued treatment or died before the first baseline imaging. |
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
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: ORR by patient subgroup

| RCC histology         | ORR, % (95% CI) |
|-----------------------|----------------|
| Papillary (n = 118)   | 28.8 (20.8 to 37.9) |
| Chromophobe (n = 21)  | 9.5 (1.2 to 30.4)  |
| Undifferentiated (n = 26) | 30.8 (14.3 to 51.8) |

| IMDC risk category    | ORR, % (95% CI) |
|-----------------------|----------------|
| Favorable (n = 53)    | 32.1 (19.9 to 46.3) |
| Intermediate or poor (n = 112) | 24.1 (16.5 to 33.1) |

| PD-L1 status         | ORR, % (95% CI) |
|----------------------|----------------|
| CPS <1 (n = 58)      | 12.1 (5.0 to 23.3) |
| CPS ≥1 (n = 102)     | 35.3 (26.1 to 45.4) |

| Sarcomatoid features (n = 38) | ORR, % (95% CI) |
|-------------------------------|----------------|
| 42.1 (26.3 to 59.2)           |                |

**FIG 3.** ORR by patient subgroup. *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.
**TABLE 3.** Treatment-Related and Immune-Mediated AEs

| AE (N = 165) | Any Grade (≥ 2 patients) | Grades 3-5 |
|--------------|--------------------------|------------|
|              | 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)
chromophobe RCC. 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. 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. 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. 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. 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%). 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

| 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)   | 2 (1.2)    |
| 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)          | 2 (1.2)    |
| Polyarthritis  | 2 (1.2)                  | 0 (0)      |
| Stomatitis     | 2 (1.2)                  | 1 (0.6)    |
| Type 1 diabetes mellitus | 2 (1.2) | 2 (1.2)    |
| Immune-mediated AEa | 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.
*aBased 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.
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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