ORIGINAL ARTICLE

Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma

B.I. Rini, E.R. Plimack, V. Stus, R. Gafanov, R. Hawkins, D. Nosov, F. Pouliot, B. Alekseev, D. Soulières, B. Melichar, I. Vynnychenko, A. Kryzhanivska, I. Bondarenko, S.J. Azevedo, D. Borchiellini, C. Szczylik, M. Markus, R.S. McDermott, J. Bedke, S. Tartas, Y.-H. Chang, S. Tamada, Q. Shou, R.F. Perini, M. Chen, M.B. Atkins, and T. Powles, for the KEYNOTE-426 Investigators*

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Rini at Cleveland Clinic Taussig Cancer Institute, 9500 Euclid Ave., Desk CA60, Cleveland, OH 44195, or at rinib2@ccf.org.

*A complete list of investigators who participated in the KEYNOTE-426 trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on February 16, 2019, at NEJM.org.

N Engl J Med 2019;380:1116-27.
DOI: 10.1056/NEJMoa1816714

ABSTRACT

BACKGROUND

The combination of pembrolizumab and axitinib showed antitumor activity in a phase 1b trial involving patients with previously untreated advanced renal-cell carcinoma. Whether pembrolizumab plus axitinib would result in better outcomes than sunitinib in such patients was unclear.

METHODS

In an open-label, phase 3 trial, we randomly assigned 861 patients with previously untreated advanced clear-cell renal-cell carcinoma to receive pembrolizumab (200 mg) intravenously once every 3 weeks plus axitinib (5 mg) orally twice daily (432 patients) or sunitinib (50 mg) orally once daily for the first 4 weeks of each 6-week cycle (429 patients). The primary end points were overall survival and progression-free survival in the intention-to-treat population. The key secondary end point was the objective response rate. All reported results are from the protocol-specified first interim analysis.

RESULTS

After a median follow-up of 12.8 months, the estimated percentage of patients who were alive at 12 months was 89.9% in the pembrolizumab–axitinib group and 78.3% in the sunitinib group (hazard ratio for death, 0.53; 95% confidence interval [CI], 0.38 to 0.74; P<0.0001). Median progression-free survival was 15.1 months in the pembrolizumab–axitinib group and 11.1 months in the sunitinib group (hazard ratio for disease progression or death, 0.69; 95% CI, 0.57 to 0.84; P<0.001). The objective response rate was 59.3% (95% CI, 54.5 to 63.9) in the pembrolizumab–axitinib group and 35.7% (95% CI, 31.1 to 40.4) in the sunitinib group (P<0.001). The benefit of pembrolizumab plus axitinib was observed across the International Metastatic Renal Cell Carcinoma Database Consortium risk groups (i.e., favorable, intermediate, and poor risk) and regardless of programmed death ligand 1 expression. Grade 3 or higher adverse events of any cause occurred in 75.8% of patients in the pembrolizumab–axitinib group and in 70.6% in the sunitinib group.

CONCLUSIONS

Among patients with previously untreated advanced renal-cell carcinoma, treatment with pembrolizumab plus axitinib resulted in significantly longer overall survival and progression-free survival, as well as a higher objective response rate, than treatment with sunitinib. (Funded by Merck Sharp & Dohme; KEYNOTE-426 ClinicalTrials.gov number, NCT02853331.)

Renal-cell carcinoma is characterized by susceptibility to both immunotherapeutic and antiangiogenic treatment approaches and resistance to cytotoxic chemotherapy.[1] Agents such as sunitinib that target the vascular endothelial growth factor (VEGF) pathway are standard first-line therapy for advanced disease.[2-7] Despite the approval of several targeted therapies by entities such as the Food and Drug Administration, the European Medicines Agency, and the Pharmaceuticals and Medical Devices Agency, the survival rate among patients with metastatic renal-cell carcinoma has plateaued.[8,9]

Both the VEGF receptor tyrosine kinase inhibitor axitinib and the anti–programmed death 1 (PD-1) monoclonal antibody pembrolizumab have shown antitumor activity in patients with previously untreated advanced clear-cell renal-cell carcinoma.[6,10] In a phase 1b trial involving patients with previously untreated metastatic renal-cell carcinoma, 73% (95% confidence interval [CI], 59 to 84) of the patients who received pembrolizumab plus axitinib had a response; 65% of patients had at least one treatment-related adverse event.[11] We conducted the KEYNOTE-426 trial to determine whether pembrolizumab plus axitinib would result in better outcomes than sunitinib in patients with previously untreated advanced renal-cell carcinoma.

Methods

Patients

Eligible patients were 18 years of age or older; had newly diagnosed or recurrent stage IV (according to the American Joint Commission on Cancer, seventh edition, classification) clear-cell renal-cell carcinoma; had received no previous systemic therapy for advanced disease; had a Karnofsky performance-status score of 70 or more (on a scale from 0 to 100, with lower scores indicating greater disability)[12]; had at least one measurable lesion as evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1[13]; and had an available tumor sample for biomarker assessment. Patients were excluded if they had symptomatic central nervous system metastases, active autoimmune disease, or poorly controlled hypertension (systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥90 mm Hg), if they had had an ischemic cardiovascular event or New York Heart Association class III or IV congestive heart failure within 1 year before screening, or if they were receiving systemic immunosuppressive treatment. Full eligibility criteria are listed in section 5.1 in the trial protocol, available with the full text of this article at NEJM.org.

Trial Design and Treatments

In this open-label, phase 3 trial, patients were randomly assigned in a 1:1 ratio to receive pembrolizumab (Keytruda, Merck Sharp & Dohme) plus axitinib (Inlyta, Pfizer) or sunitinib (Sutent, Pfizer). Randomization was stratified according to International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk group (favorable, intermediate, or poor risk) and geographic region (North America, Western Europe, or the rest of the world). Favorable risk corresponds to an IMDC score of 0, intermediate risk to a score of 1 or 2, and poor risk to a score of 3 to 6.[14] IMDC risk score is determined by the total number of the following six risk factors that are present: Karnofsky performance-status score of less than 80, time from initial diagnosis to randomization of less than 1 year, hemoglobin level below the lower limit of the normal range, corrected serum calcium level above the upper limit of the normal range, absolute neutrophil count above the upper limit of the normal range, and platelet count above the upper limit of the normal range.[14]

Pembrolizumab was administered intravenously at a dose of 200 mg once every 3 weeks. Axitinib was administered orally at a dose of 5 mg twice daily; the dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met and reduced to 3 mg, then 2 mg, twice daily to manage toxic effects. Sunitinib was administered orally at a dose of 50 mg daily for the first 4 weeks of each 6-week cycle; the dose could be reduced to 37.5 mg, then 25 mg, for the first 4 weeks of each 6-week cycle to manage toxic effects. Treatment was continued until disease progression, development of unacceptable toxic effects, or physician or patient decision to discontinue. Pembrolizumab was administered for a maximum of 35 cycles. Patients who had a confirmed complete response could discontinue treatment. Patients with unconfirmed disease progression who were in clinically stable condition could continue to receive treatment at the

discretion of the investigator until progression was confirmed by means of subsequent imaging performed at least 28 days after radiographic progression was first observed; patients could be treated beyond confirmed progression if prespecified criteria were met. If one drug in the pembrolizumab–axitinib group was discontinued because of toxic effects, the other drug could be continued. Full guidelines regarding treatment decisions and management of adverse events are provided in section 5.2 in the protocol.

END POINTS AND ASSESSMENTS

The dual primary end points were overall survival and progression-free survival according to RECIST, version 1.1, as determined by blinded, independent central review. The key secondary end point was the objective response rate according to RECIST, version 1.1, as determined by blinded, independent central review. Other secondary end points included duration of response and safety. Efficacy was assessed in the intention-to-treat population, which included all patients who underwent randomization. Safety was assessed in the as-treated population, which included all randomly assigned patients who received one or more doses of trial treatment.

Data on adverse events and laboratory abnormalities were collected regularly throughout the treatment period and for 30 days thereafter (data on serious adverse events and events of interest were collected for 90 days after the end of the treatment period) and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Tumor imaging was performed at baseline and week 12 and then every 6 weeks through week 54 and every 12 weeks thereafter. Bone scans were required at baseline. If the baseline bone scan was positive, additional scans were performed at week 18 and then every 12 weeks through week 54 and every 24 weeks thereafter. Response was assessed according to RECIST, version 1.1.[13] Patients were contacted for assessment of survival every 12 weeks during follow-up. Programmed death ligand 1 (PD-L1) expression in archival or newly obtained, formalin-fixed tumor samples was assessed at a central laboratory with the use of the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies) and was characterized according to the combined positive score, which was calculated as the number of PD-L1–positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells, multiplied by 100.

TRIAL OVERSIGHT

The trial was designed by academic advisors and employees of the sponsor. An independent data and safety monitoring committee oversaw the trial, periodically assessed safety, and assessed efficacy at the prespecified interim analysis. The trial protocol and all amendments were approved by the appropriate ethics body at each center. All patients provided written informed consent before enrollment.

The trial was conducted in accordance with Good Clinical Practice guidelines. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol and attest that they had access to the data and that they participated in writing or reviewing and editing drafts of the manuscript. As part of the site agreement, investigators agreed to keep all aspects of the trial, including the data, confidential. Assistance with the preparation of the manuscript was provided by a medical writer employed by the sponsor.

STATISTICAL ANALYSIS

The Kaplan–Meier method was used to estimate overall survival, progression-free survival, and duration of response. The stratified log-rank test was used to assess between-group differences in overall survival and progression-free survival. A stratified Cox proportional-hazards model and Efron's method of handling ties were used to assess the magnitude of the treatment difference. The stratified method of Miettinen and Nurminen with weights proportional to the stratum size was used to assess the difference in response rate. The stratification factors used at randomization were applied to all stratified analyses.

The full statistical analysis plan is available in section 8.0 in the protocol. The graphical method of Maurer and Bretz was used to control the family-wise type I error rate at a one-sided alpha level of 0.025 across all hypotheses and interim analyses. We estimated that with enrollment of 861 patients, the trial would have 99% power to detect a hazard ratio for disease progression or death of 0.60 for the comparison of pembrolizumab plus axitinib with sunitinib, at a one-sided

Table 1. Demographic and Disease Characteristics at Baseline.*

Characteristic	Pembrolizumab–Axitinib (N=432)	Sunitinib (N=429)
Age		
Median (range) — yr	62 (30–89)	61 (26–90)
<65 yr — no. (%)	260 (60.2)	278 (64.8)
Male sex — no. (%)	308 (71.3)	320 (74.6)
Region of enrollment — no. (%)		
North America	104 (24.1)	103 (24.0)
Western Europe	106 (24.5)	104 (24.2)
Rest of the world	222 (51.4)	222 (51.7)
IMDC prognostic risk — no. (%)†		
Favorable	138 (31.9)	131 (30.5)
Intermediate	238 (55.1)	246 (57.3)
Poor	56 (13.0)	52 (12.1)
Sarcomatoid features — no./total no. with known status (%)	51/285 (17.9)	54/293 (18.4)
PD-L1 combined positive score — no./total no. with data (%)‡		
≥1	243/410 (59.3)	254/412 (61.7)
<1	167/410 (40.7)	158/412 (38.3)
No. of organs with metastases — no. (%)§		
1	114 (26.4)	96 (22.4)
≥2	315 (72.9)	331 (77.2)
Most common sites of metastasis — no. (%)¶		
Lung	312 (72.2)	309 (72.0)
Lymph node	199 (46.1)	197 (45.9)
Bone	103 (23.8)	103 (24.0)
Adrenal gland	67 (15.5)	76 (17.7)
Liver	66 (15.3)	71 (16.6)
Previous radiotherapy — no. (%)	41 (9.5)	40 (9.3)
Previous nephrectomy — no. (%)	357 (82.6)	358 (83.4)

* There were no significant differences between groups, at a two-sided alpha level of 0.05. Percentages may not total 100 because of rounding.
† Favorable risk corresponds to an International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) score of 0, intermediate risk to a score of 1 or 2, and poor risk to a score of 3 to 6. IMDC risk score is determined by the total number of the following six risk factors that are present: Karnofsky performance-status score of less than 80 (on a scale from 0 to 100, with lower scores indicating greater disability[12]), a time from initial diagnosis to randomization of less than 1 year, a hemoglobin level below the lower limit of the normal range, a corrected serum calcium level above the upper limit of the normal range, an absolute neutrophil count above the upper limit of the normal range, and platelet count above the upper limit of the normal range.[14]
‡ The programmed death ligand 1 (PD-L1) combined positive score was calculated as the number of PD-L1–positive cells (tumor cells, lymphocytes, and macrophages) divided by total number of tumor cells, multiplied by 100.
§ Information on the number of organs with target and nontarget lesions was missing for three patients (0.7%) in the pembrolizumab–axitinib group and for two patients (0.5%) in the sunitinib group.
¶ A post hoc Stouffer's test, which tests for imbalances between groups, suggested that random assignment resulted in near-perfect balance between treatment groups in the sites of metastasis. A review of randomization procedures did not reveal any aberrations.

alpha level of 0.002, assuming 487 instances of disease progression or death and one interim analysis (performed after approximately 75% of the target number of events had occurred) and 80% power to detect a hazard ratio for death of 0.75, at a one-sided alpha level of 0.023, assum-

ing 404 deaths and two interim analyses (performed after approximately 48% of the target number of deaths had occurred for the first interim analysis and 74% of the target number of deaths had occurred for the second interim analysis). The first interim analysis was to be performed at least 7 months after the last patient underwent randomization and after at least 305 instances of disease progression or death had been observed; it was estimated that approximately 195 deaths would be observed at this time. At the cutoff date for the first interim analysis (August 24, 2018), a total of 395 patients had disease progression or had died, and 156 deaths had occurred; the one-sided P value thresholds for declaring the superiority of pembrolizumab plus axitinib over sunitinib were 0.0001 for overall survival and 0.0013 for progression-free survival; if the overall and progression-free survival thresholds were met, response rate could be tested at a one-sided alpha level of 0.025. All data reported here are based on the first interim analysis.

Figure 1 (facing page). Overall Survival in the Intention-to-Treat Population.

Panel A shows the Kaplan–Meier estimates of overall survival. Tick marks in Panel A represent data censored at the last time the patient was known to be alive. Panel B shows the analysis of overall survival in subgroups. Analyses were performed with the use of a Cox regression model, with treatment used as a covariate, stratified according to International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk category and geographic region. Karnofsky performance-status scores range from 0 to 100, with lower scores indicating greater disability.[12] The programmed death ligand 1 (PD-L1) combined positive score was calculated as the number of PD-L1–positive cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells, multiplied by 100; patients with PD-L1 expression that could not be evaluated were excluded from the analysis of the subgroup defined according to PD-L1 combined positive score.

RESULTS

PATIENTS AND TREATMENTS

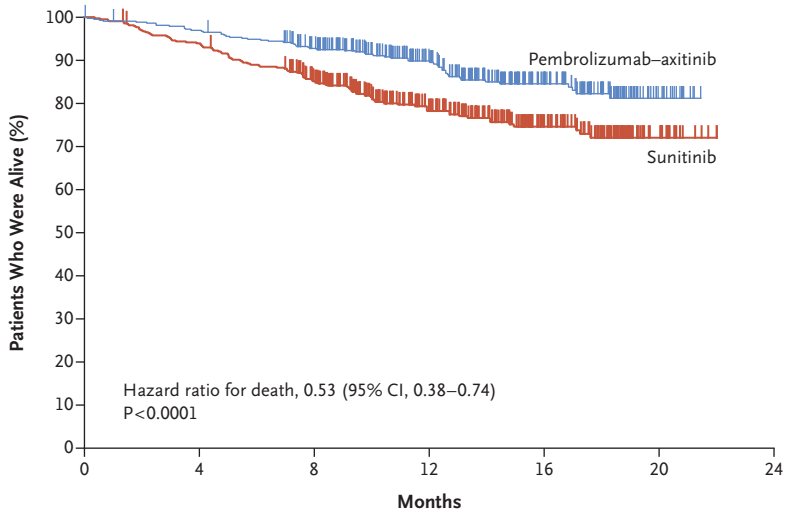
A total of 1062 patients at 129 sites in 16 countries were screened for eligibility; of these, 861 patients at 124 sites underwent randomization from October 24, 2016, to January 24, 2018. A total of 432 patients were assigned to the pembrolizumab–axitinib group, and 429 patients were assigned to the sunitinib group (Fig. S1 in the Supplementary Appendix, available at NEJM .org). Baseline demographics and disease characteristics were as expected for a trial involving patients with advanced renal-cell carcinoma and were balanced between the groups (Table 1). The IMDC risk category was favorable for 31.2% of patients, intermediate for 56.2%, and poor for 12.5%. Among the 822 patients with tumor samples that could be evaluated for PD-L1 expression, 60.5% had a combined positive score of 1 or more.

A total of 429 patients in the pembrolizumab–axitinib group and 425 patients in the sunitinib group received at least one dose of the assigned treatment. The median duration of any treatment was 10.4 months (range, 0.03 to 21.2) in the pembrolizumab–axitinib group and 7.8 months (range, 0.07 to 20.5) in the sunitinib group. In the pembrolizumab–axitinib group, the median duration of treatment was 8.3 months with pembrolizumab and axitinib, 9.2 months with pembrolizumab, and 9.6 months with axitinib. The median daily dose of axitinib was 9.8 mg, and the median daily dose of sunitinib was 50.0 mg. Median follow-up (defined as the time from randomization to death or the date of data cutoff for those who were alive) was 12.8 months (range, 0.1 to 22.0) in the intention-to-treat population. In the as-treated population, 253 of the 429 patients (59.0%) in the pembrolizumab–axitinib group and 183 of the 425 patients (43.1%) in the sunitinib group were still receiving the trial treatment. The most common reason for treatment discontinuation was disease progression (Fig. S1 in the Supplementary Appendix). In the pembrolizumab–axitinib group, 88 patients (50.0% of the 176 patients who discontinued pembrolizumab plus axitinib) received subsequent anticancer therapy, most commonly a VEGF or VEGF receptor inhibitor (44.3%). In the sunitinib group, 147 patients (60.7% of the 242 patients who discontinued sunitinib) received subsequent anticancer therapy, most commonly a PD-1 or PD-L1 inhibitor (37.6%) (Table S1 in the Supplementary Appendix).

EFFICACY

The estimated percentage of patients who were alive at 12 months was 89.9% (95% CI, 86.4 to 92.4) in the pembrolizumab–axitinib group and 78.3% (95% CI, 73.8 to 82.1) in the sunitinib

A Overall Survival



No. at Risk

Pembrolizumab–axitinib	432	417	378	256	136	18	0
Sunitinib	429	401	341	211	110	20	0

B Overall Survival According to Subgroup

Subgroup	No. of Deaths/ No. of Patients	Hazard Ratio for Death (95% CI)
Overall	156/861	0.53 (0.38–0.74)
Age		
<65 yr	91/538	0.47 (0.30–0.73)
≥65 yr	65/323	0.59 (0.36–0.97)
Sex		
Male	108/628	0.54 (0.37–0.80)
Female	48/233	0.45 (0.25–0.83)
Region of enrollment		
North America	31/207	0.69 (0.34–1.41)
Western Europe	31/210	0.46 (0.22–0.97)
Rest of the world	94/444	0.51 (0.33–0.77)
IMDC risk category		
Favorable	17/269	0.64 (0.24–1.68)
Intermediate	93/484	0.53 (0.35–0.82)
Poor	46/108	0.43 (0.23–0.81)
Karnofsky performance-status score		
90 or 100	88/688	0.53 (0.35–0.82)
70 or 80	67/172	0.49 (0.30–0.81)
PD-L1 combined positive score		
<1	54/325	0.59 (0.34–1.03)
≥1	90/497	0.54 (0.35–0.84)
No. of organs with metastases		
1	21/210	0.20 (0.07–0.57)
≥2	134/646	0.60 (0.42–0.85)

group. The corresponding estimates for 18 months were 82.3% (95% CI, 77.2 to 86.3) and 72.1% (95% CI, 66.3 to 77.0) (Fig. 1A). The median survival was not reached in either group. The risk of death was 47% lower in the pembrolizumab–axitinib group than in the sunitinib group (hazard ratio for death, 0.53; 95% CI, 0.38 to 0.74; P<0.0001). The median progression-free

survival was 15.1 months (95% CI, 12.6 to 17.7) in the pembrolizumab–axitinib group and 11.1 months (95% CI, 8.7 to 12.5) in the sunitinib group (Fig. 2A). The hazard ratio for disease progression or death was 0.69 (95% CI, 0.57 to 0.84; P<0.001). The benefits of pembrolizumab plus axitinib with respect to overall survival and progression-free survival were observed in all subgroups examined, including all IMDC risk and PD-L1 expression categories (Figs. 1B and 2B, and Table S2 in the Supplementary Appendix).

The objective response rate was 59.3% (95% CI, 54.5 to 63.9) in the pembrolizumab–axitinib group and 35.7% (95% CI, 31.1 to 40.4) in the sunitinib group (P<0.001); 5.8% of patients in the pembrolizumab–axitinib group and 1.9% in the sunitinib group had a complete response (Table 2). The median duration of response was not reached in the pembrolizumab–axitinib group (range, 1.4+ to 18.2+ months), and the median duration of response was 15.2 months (range, 1.1+ to 15.4+) in the sunitinib group (with plus signs in the ranges indicating an ongoing response at the time of data cutoff). The estimated percentage of patients with an ongoing response at 1 year was 70.6% in the pembrolizumab–axitinib group and 61.6% in the sunitinib group (Fig. S2 in the Supplementary Appendix).

Figure 2 (facing page). Progression-free Survival in the Intention-to-Treat Population.

Panel A shows the Kaplan–Meier estimates of progression-free survival. Tick marks in Panel A represent data censored at the last time the patient was known to be alive and free from disease progression (i.e., at the time of the last imaging assessment). Panel B shows the analysis of progression-free survival in subgroups. Progression-free survival was assessed according to Response Evaluation Criteria in Solid Tumors, version 1.1, by means of blinded, independent central review of radiologic imaging. All analyses were based on a Cox regression model, with treatment used as a covariate, stratified according to IMDC risk category and geographic region. Patients with PD-L1 expression that could not be evaluated were excluded from the analysis of subgroup defined according to PD-L1 combined positive score.

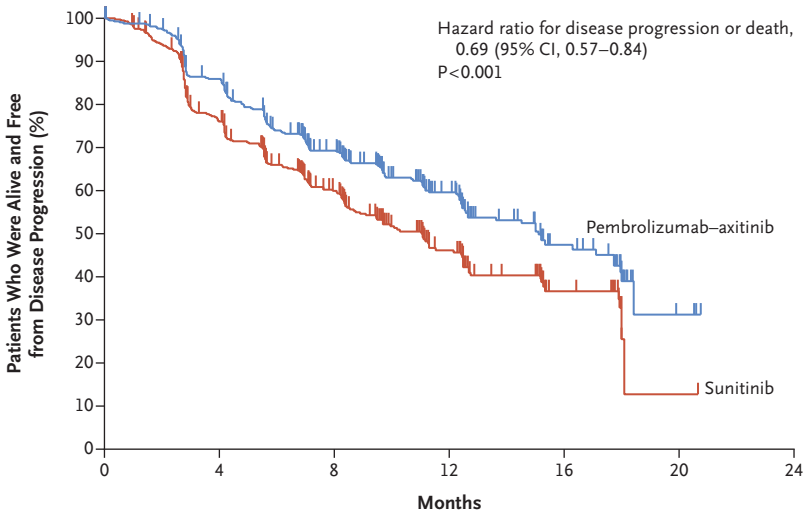
SAFETY

Adverse events of any cause occurred in 98.4% of the 429 patients in the pembrolizumab–axitinib group who received the assigned treatment and in 99.5% of the 425 patients in the sunitinib group who received the assigned treatment. These events were of grade 3 or higher in 75.8% of the patients in the pembrolizumab–axitinib group and in 70.6% of the patients in the sunitinib group; 62.9% of the patients in the pembrolizumab–axitinib group and 58.1% of the patients in the sunitinib group had events of grade 3 or higher that were attributed by the investigator to trial treatment. In the pembrolizumab–axitinib group, adverse events of any cause led to discontinuation of either drug in 30.5% of patients, discontinuation of both drugs in 10.7%, interruption of either drug in 69.9%, and dose reduction of axitinib in 20.3%. The median time to discontinuation of both pembrolizumab and axitinib because of adverse events of any cause was 105.5 days, and the median time to discontinuation of pembrolizumab because of adverse events of any cause was 65 days. In the sunitinib group, adverse events of any cause led to discontinuation in 13.9% of patients, interruption in 49.9%, and dose reduction in 30.1%. A summary of treatment-related adverse events is provided in Table S3 in the Supplementary Appendix. Of the 11 patients (2.6%) in the pembrolizumab–axitinib group who died from adverse events, 4 (0.9%) died from treatment-related adverse events (from myasthenia gravis, myocarditis, necrotizing fasciitis, and pneumonitis, in 1 patient each). Among the 15 patients (3.5%) in the sunitinib group who died from adverse events, 7 patients (1.6%) died from treatment-related adverse events (from acute myocardial infarction, cardiac arrest, fulminant hepatitis, gastrointestinal hemorrhage, intracranial hemorrhage, malignant neoplasm progression, and pneumonia, in 1 patient each).

In both groups, the most common adverse events of any cause and the most common adverse events related to treatment were diarrhea and hypertension (Table 3, and Table S3 in the Supplementary Appendix). The between-group difference in the risk of adverse events of grade 3 or higher that occurred in at least 10% of patients is provided in Figure S3 in the Supplementary Appendix. Adverse events of grade 3 or higher that occurred in 10% or more of patients were hypertension and increased alanine aminotransferase levels in the pembrolizumab–axitinib group and hypertension in the sunitinib group.

Adverse events of interest, which were determined on the basis of a list of terms specified by the sponsor and were considered regardless of whether the investigator determined that they were related to treatment, occurred in 51.3% of

A Progression-free Survival

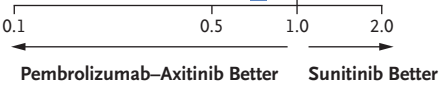


No. at Risk

Pembrolizumab–axitinib	432	357	251	140	42	3	0
Sunitinib	429	302	193	89	29	1	0

B Progression-free Survival According to Subgroup

Subgroup	No. of Instances of Disease Progression or Death/No. of Patients	Hazard Ratio for Disease Progression or Death (95% CI)
Overall	395/861	0.69 (0.57–0.84)
Age		
<65 yr	248/538	0.70 (0.54–0.90)
≥65 yr	147/323	0.63 (0.45–0.88)
Sex		
Male	287/628	0.77 (0.61–0.97)
Female	108/233	0.54 (0.37–0.81)
Region of enrollment		
North America	75/207	0.79 (0.50–1.25)
Western Europe	97/210	0.59 (0.39–0.89)
Rest of the world	223/444	0.71 (0.54–0.92)
IMDC risk category		
Favorable	90/269	0.81 (0.53–1.24)
Intermediate	232/484	0.70 (0.54–0.91)
Poor	73/108	0.58 (0.35–0.94)
Karnofsky performance-status score		
90 or 100	292/688	0.69 (0.54–0.87)
70 or 80	102/172	0.67 (0.45–1.00)
PD-L1 combined positive score		
<1	137/325	0.87 (0.62–1.23)
≥1	240/497	0.62 (0.47–0.80)
No. of organs with metastases		
1	75/210	0.54 (0.33–0.87)
≥2	317/646	0.73 (0.58–0.91)



patients in the pembrolizumab–axitinib group and in 36.2% of patients in the sunitinib group (Table S4 in the Supplementary Appendix). Grade 3 events occurred in 8.4% of patients in the pembrolizumab–axitinib group and in 1.6% in the sunitinib group, grade 4 events occurred

Table 2. Summary of Confirmed Objective Response.*

Variable	Pembrolizumab–Axitinib (N=432)	Sunitinib (N=429)
Objective response rate — % (95% CI)†	59.3 (54.5 to 63.9)	35.7 (31.1 to 40.4)
Best overall response — no. (%)		
Complete response	25 (5.8)	8 (1.9)
Partial response	231 (53.5)	145 (33.8)
Stable disease	106 (24.5)	169 (39.4)
Progressive disease	47 (10.9)	73 (17.0)
Could not be evaluated‡	8 (1.9)	6 (1.4)
Not assessed§	15 (3.5)	28 (6.5)
Median time to response (range) — mo¶	2.8 (1.5 to 16.6)	2.9 (2.1 to 15.1)
Median duration of response (range) — mo‖	Not reached (1.4+ to 18.2+)	15.2 (1.1+ to 15.4+)

* Response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, by means of blinded, independent central review of radiologic imaging. Percentages may not total 100 because of rounding.
† The estimated treatment difference in objective response between the pembrolizumab–axitinib group and the sunitinib group was 23.6 percentage points (95% CI, 17.2 to 29.9; P<0.001) and was calculated with the use of the method of Miettinen and Nurminen and stratified according to IMDC risk group[14] (favorable, intermediate, or poor) and geographic region (North America, Western Europe, or the rest of the world).
‡ The patients who could not be evaluated included those who had one or more postbaseline imaging assessments, none of which could be evaluated for response according to RECIST, version 1.1.
§ The patients who were not assessed included those who did not have any postbaseline imaging assessments.
¶ The median time to response was calculated only for patients who had a complete or partial response (256 patients in the pembrolizumab–axitinib group and 153 patients in the sunitinib group).
‖ The median duration of response was calculated with the use of the Kaplan–Meier method with data from patients who had a complete or partial response (256 patients in the pembrolizumab–axitinib group and 153 patients in the sunitinib group). Plus signs in the ranges indicate responses that were ongoing at the time of data cutoff.

in 1.6% and 0%, respectively, and grade 5 events occurred in 0.7% and 0.2%, respectively.

DISCUSSION

The results of this randomized, phase 3 trial of patients with previously untreated advanced renal-cell carcinoma showed that treatment with pembrolizumab plus axitinib resulted in a 47% lower risk of death and a 31% lower risk of disease progression or death than treatment with sunitinib. The objective response rate was 23.6 percentage points higher in the pembrolizumab–axitinib group than in the sunitinib group. Although subgroup analyses should be considered hypothesis-generating only, it is notable that the benefit of pembrolizumab plus axitinib was observed across all subgroups tested, including in all IMDC risk groups and both in patients who had tumors with PD-L1 expression and those who had tumors without PD-L1 expression. These data build on the single-agent activity of pembrolizumab and axitinib.[6,10] The significant overall survival advantage is particularly notable because it has not been achieved with first-line treatment of renal-cell carcinoma with the use of anti–VEGF-based therapy administered alone or in combination.[2-7,15]

Results of other trials have also suggested that combination therapy with a checkpoint-inhibitor backbone has anticancer activity as first-line therapy in patients with advanced renal-cell carcinoma. Among patients who had intermediate or poor risk according to the IMDC criteria, a combination of the PD-1 inhibitor nivolumab and the cytotoxic T-lymphocyte–associated protein 4 inhibitor ipilimumab resulted in longer overall survival and a higher objective response rate (the primary end points) than sunitinib; nivolumab plus ipilimumab also resulted in a complete response in 9% of patients.[16] An exploratory analysis involving patients with favorable risk showed that sunitinib resulted in longer progression-free survival and a higher objective response rate than nivolumab plus ipilimumab. The combination of the PD-L1 inhibitor avelumab and axitinib resulted in longer progression-free survival and a higher objective response rate than sunitinib among patients with previously untreated PD-L1–positive disease.[17] Additional follow-up

Table 3. Adverse Events of Any Cause That Occurred in 10% or More of Patients in the As-Treated Population.*

Event	Pembrolizumab–Axitinib (N=429)		Sunitinib (N=425)	
	Any Grade	Grade 3, 4, or 5†	Any Grade	Grade 3, 4, or 5‡
	number of patients (percent)			
Diarrhea	233 (54.3)	39 (9.1)	191 (44.9)	20 (4.7)
Hypertension	191 (44.5)	95 (22.1)	193 (45.4)	82 (19.3)
Fatigue	165 (38.5)	12 (2.8)	161 (37.9)	28 (6.6)
Hypothyroidism	152 (35.4)	1 (0.2)	134 (31.5)	1 (0.2)
Decreased appetite	127 (29.6)	12 (2.8)	125 (29.4)	3 (0.7)
Palmar–plantar erythrodysesthesia syndrome	120 (28.0)	22 (5.1)	170 (40.0)	16 (3.8)
Nausea	119 (27.7)	4 (0.9)	134 (31.5)	4 (0.9)
Alanine aminotransferase increased	115 (26.8)	57 (13.3)	64 (15.1)	13 (3.1)
Aspartate aminotransferase increased	112 (26.1)	30 (7.0)	69 (16.2)	10 (2.4)
Dysphonia	109 (25.4)	1 (0.2)	14 (3.3)	0
Cough	91 (21.2)	1 (0.2)	58 (13.6)	2 (0.5)
Constipation	89 (20.7)	0	62 (14.6)	1 (0.2)
Arthralgia	78 (18.2)	4 (0.9)	26 (6.1)	3 (0.7)
Weight decreased	76 (17.7)	13 (3.0)	47 (11.1)	1 (0.2)
Proteinuria	75 (17.5)	12 (2.8)	47 (11.1)	6 (1.4)
Dyspnea	69 (16.1)	7 (1.6)	46 (10.8)	5 (1.2)
Headache	68 (15.9)	4 (0.9)	69 (16.2)	2 (0.5)
Stomatitis	67 (15.6)	3 (0.7)	89 (20.9)	9 (2.1)
Asthenia	65 (15.2)	11 (2.6)	63 (14.8)	13 (3.1)
Pruritus	65 (15.2)	1 (0.2)	25 (5.9)	0
Vomiting	65 (15.2)	1 (0.2)	79 (18.6)	4 (0.9)
Rash	61 (14.2)	1 (0.2)	47 (11.1)	2 (0.5)
Back pain	57 (13.3)	4 (0.9)	43 (10.1)	7 (1.6)
Mucosal inflammation	57 (13.3)	4 (0.9)	93 (21.9)	8 (1.9)
Hyperthyroidism	55 (12.8)	5 (1.2)	16 (3.8)	0
Pyrexia	55 (12.8)	0	43 (10.1)	0
Pain in extremity	51 (11.9)	4 (0.9)	42 (9.9)	4 (0.9)
Abdominal pain	49 (11.4)	5 (1.2)	29 (6.8)	1 (0.2)
Blood creatinine increased	48 (11.2)	2 (0.5)	51 (12.0)	3 (0.7)
Dysgeusia	47 (11.0)	1 (0.2)	131 (30.8)	0
Anemia	34 (7.9)	3 (0.7)	100 (23.5)	21 (4.9)
Dyspepsia	22 (5.1)	0	62 (14.6)	1 (0.2)
Gastroesophageal reflux disease	18 (4.2)	0	48 (11.3)	3 (0.7)
Platelet count decreased	16 (3.7)	1 (0.2)	77 (18.1)	31 (7.3)
Thrombocytopenia	11 (2.6)	0	99 (23.3)	25 (5.9)
Neutropenia	8 (1.9)	1 (0.2)	82 (19.3)	28 (6.6)
Neutrophil count decreased	4 (0.9)	1 (0.2)	50 (11.8)	29 (6.8)
White-cell count decreased	2 (0.5)	0	43 (10.1)	12 (2.8)

* Shown are all adverse events that occurred while patients were receiving the assigned treatment or within 30 days after the end of the trial treatment period (or, for serious events, within 90 days after the end of the trial treatment period). The as-treated population included all patients who underwent randomization and received at least one dose of trial treatment. Events are listed in descending order of frequency in the pembrolizumab–axitinib group. Adverse events are classified according to the *Medical Dictionary for Regulatory Activities*, version 21.0.

† In the pembrolizumab–axitinib group, 11 patients (2.6%) died from an adverse event: 1 patient each from cardiac arrest, myasthenia gravis, myocarditis, necrotizing fasciitis, plasma-cell myeloma, pneumonitis, pulmonary embolism, pulmonary thrombosis, respiratory failure, sudden cardiac death, and death not otherwise specified.

‡ In the sunitinib group, 15 patients (3.5%) died from an adverse event: 2 patients from pneumonia, 1 patient from both pneumonia and cardiac amyloidosis, and 1 patient each from acute myocardial infarction, cardiac arrest, chronic cardiac failure, fulminant hepatitis, gastric hemorrhage, gastrointestinal hemorrhage, intracranial hemorrhage, malignant neoplasm progression, sepsis, sudden death, urinary tract infection, and death not otherwise specified.

is required to determine whether avelumab plus axitinib will improve overall survival. The combination of the PD-L1 inhibitor atezolizumab with the anti-VEGF monoclonal antibody bevacizumab resulted in longer progression-free survival and fewer grade 3 or 4 treatment-related adverse events than sunitinib among patients with previously untreated PD-L1–positive disease.[18]

The observed safety profiles of pembrolizumab plus axitinib and of sunitinib were as expected on the basis of the known profiles of these three drugs, although the incidence of grade 3 or 4 elevations in liver-enzyme levels in the pembrolizumab–axitinib group was higher than previously observed when each agent was used as monotherapy.[19,20] There were no deaths related to hepatic adverse events in the pembrolizumab–axitinib group. Further characterization of hepatic adverse events in this trial is ongoing. Discontinuation of any treatment because of adverse events occurred more frequently in the pembrolizumab–axitinib group than in the sunitinib group. The incidence and severity of adverse events of interest were as expected on the basis of previous experience with pembrolizumab monotherapy.[10,19] The exception is a greater incidence of hyperthyroidism and of hypothyroidism, which was not unexpected given that thyroid abnormalities are also a known side effect of axitinib.[20]

A limitation of our trial was the short duration of follow-up. Because of this, the number of deaths that accrued in certain subgroups was small, which led to large confidence intervals around the point estimates. The short duration of follow-up may also mean that responses, including complete responses, are still evolving. No further alpha-controlled efficacy testing will be performed because the protocol-specified criteria for declaring a significant benefit of pembrolizumab plus axitinib as compared with sunitinib were met. However, patients will continue to be followed for assessment of efficacy and safety.

In conclusion, the results of the KEYNOTE-426 trial showed that among patients with previously untreated advanced renal-cell carcinoma, treatment with pembrolizumab plus axitinib resulted in significantly longer overall survival and progression-free survival and a significantly higher objective response rate than sunitinib alone. The hepatic toxic effects of pembrolizumab plus axitinib require further examination, but the overall frequency of toxic effects was similar in the two groups. The benefit of pembrolizumab plus axitinib was observed across all IMDC prognostic risk categories and in both PD-L1 expression subgroups.

Supported by Merck Sharp & Dohme. Axitinib and sunitinib were provided by Pfizer.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients and their families and caregivers for participating in this trial, all the investigators and site personnel, and the following employees of Merck Sharp & Dohme: Scot Ebbinghaus for critical review of an earlier version of the manuscript; Markus Puhlmann for input into the trial design and critical review of an earlier version of the manuscript; Sabrina Shuyan Wan for statistical expertise and input into the trial design; Huan Huang for statistical programming support; Carolina Buitrago Jiménez, Kristin Canchola, Fonati Collins, Lori DeMauro, Sima Gaile, Yuying Hwang, Lynn Hyde, Karen Muldowney, Luisa Padilla, and Cynthia Silber for support of trial conduct; and Melanie A. Leiby for medical writing and editorial assistance.

APPENDIX

The authors' full names and academic degrees are as follows: Brian I. Rini, M.D., Elizabeth R. Plimack, M.D., Viktor Stus, M.D., Ph.D., Rustem Gafanov, M.D., Robert Hawkins, M.B., B.S., Ph.D., Dmitry Nosov, M.D., D.Sci., Frédéric Pouliot, M.D., Ph.D., Boris Alekseev, M.D., Denis Soulières, M.D., Bohuslav Melichar, M.D., Ph.D., Ihor Vynnychenko, M.D., Ph.D., Anna Kryzhanivska, M.D., Igor Bondarenko, M.D., Sergio J. Azevedo, M.D., Delphine Borchiellini, M.D., Cezary Szczylik, M.D., Ph.D., Maurice Markus, M.D., Ph.D., Raymond S. McDermott, M.D., Jens Bedke, M.D., Sophie Tartas, M.D., Yen-Hwa Chang, M.D., Ph.D., Satoshi Tamada, M.D., Ph.D., Qiong Shou, Ph.D., Rodolfo F. Perini, M.D., Mei Chen, M.D., Ph.D., Michael B. Atkins, M.D., and Thomas Powles, M.D.

From the Cleveland Clinic Taussig Cancer Institute, Cleveland (B.I.R.); Fox Chase Cancer Center, Philadelphia (E.R.P.); Dnipropetrovsk Medical Academy of Ministry of Health of Ukraine (V.S.) and Dnipropetrovsk Medical Academy (I.B.), Dnipro, Sumy State University, Sumy Regional Oncology Center, Sumy (I.V.), and Ivano-Frankivsk National Medical University, Ivano-Frankivsk (A.K.) — all in Ukraine; the Russian Scientific Center of Roentgen Radiology (R.G.), Central Clinical Hospital with Outpatient Clinic (D.N.), and Hertzen Moscow Cancer Research Institute (B.A.), Moscow; the Christie NHS Foundation Trust, Manchester (R.H.), and Barts Health and the Royal Free NHS Trusts, Barts Cancer Institute, and Queen Mary University of London, London (T.P.) — all in the United Kingdom; Centre Hospitalier Universitaire (CHU) de Québec and Université Laval, Quebec, QC (F.P.), and CHU de Montréal, Montreal (D.S.) — both in Canada; Palacký University Medical School and Teaching Hospital, Olomouc, Czech Republic (B.M.); Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil (S.J.A.); Centre Antoine Lacassagne, Université Côte d'Azur, Nice (D.B.), and Hôpitaux Universitaires de Lyon, Lyon (S. Tartas) — both in France; Military Institute of Medicine, Warsaw, Poland (C.S.); Rocky Mountain Cancer Center, Colorado Springs, CO (M.M.); Adelaide and Meath Hospital and University College Dublin, Dublin (R.S.M.); the Department of Urology, Eberhard-Karls University Tübingen, Tübingen, Germany (J.B.); Taipei Veterans General Hospital, Taipei, Taiwan (Y.-H.C.); Osaka City University Hospital, Osaka, Japan (S. Tamada); MSD China, Beijing (Q.S.); Merck, Kenilworth, NJ (R.F.P., M.C.); and Georgetown Lombardi Comprehensive Cancer Center, Washington, DC (M.B.A.).

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