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Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma

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ABSTRACT

BACKGROUND

Lenvatinib in combination with pembrolizumab or everolimus has activity against advanced renal cell carcinoma. The efficacy of these regimens as compared with that of sunitinib is unclear.

METHODS

In this phase 3 trial, we randomly assigned (in a 1:1:1 ratio) patients with advanced renal cell carcinoma and no previous systemic therapy to receive lenvatinib (20 mg orally once daily) plus pembrolizumab (200 mg intravenously once every 3 weeks), lenvatinib (18 mg orally once daily) plus everolimus (5 mg orally once daily), or sunitinib (50 mg orally once daily, alternating 4 weeks receiving treatment and 2 weeks without treatment). The primary end point was progression-free survival, as assessed by an independent review committee in accordance with Response Evaluation Criteria in Solid Tumors, version 1.1. Overall survival and safety were also evaluated.

RESULTS

A total of 1069 patients were randomly assigned to receive lenvatinib plus pembrolizumab (355 patients), lenvatinib plus everolimus (357), or sunitinib (357). Progression-free survival was longer with lenvatinib plus pembrolizumab than with sunitinib (median, 23.9 vs. 9.2 months; hazard ratio for disease progression or death, 0.39; 95% confidence interval [CI], 0.32 to 0.49; P<0.001) and was longer with lenvatinib plus everolimus than with sunitinib (median, 14.7 vs. 9.2 months; hazard ratio, 0.65; 95% CI, 0.53 to 0.80; P<0.001). Overall survival was longer with lenvatinib plus pembrolizumab than with sunitinib (hazard ratio for death, 0.66; 95% CI, 0.49 to 0.88; P=0.005) but was not longer with lenvatinib plus everolimus than with sunitinib (hazard ratio, 1.15; 95% CI, 0.88 to 1.50; P=0.30). Grade 3 or higher adverse events emerged or worsened during treatment in 82.4% of the patients who received lenvatinib plus pembrolizumab, 83.1% of those who received lenvatinib plus everolimus, and 71.8% of those who received sunitinib. Grade 3 or higher adverse events occurring in at least 10% of the patients in any group included hypertension, diarrhea, and elevated lipase levels.

CONCLUSIONS

Lenvatinib plus pembrolizumab was associated with significantly longer progression-free survival and overall survival than sunitinib. (Funded by Eisai and Merck Sharp and Dohme; CLEAR ClinicalTrials.gov number, NCT02811861.)

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*A full list of the CLEAR Trial Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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First-line treatment with vascular endothelial growth factor receptor tyrosine kinase inhibitors has been shown to provide benefits for patients with advanced renal cell carcinoma, but most patients have disease relapse as resistance develops.[1,2] Treatment with immune-checkpoint inhibitors, either as a dual-type combination (e.g., nivolumab plus ipilimumab) or in combination with kinase inhibitors (e.g., pembrolizumab or avelumab plus axitinib, or cabozantinib plus nivolumab), has provided better outcomes than sunitinib for patients with metastatic renal cell carcinoma.[3-8] These regimens are now recommended as standard-of-care options,[9,10] and more combination strategies are being explored.

Lenvatinib, an antiangiogenic agent, and pembrolizumab, an anti–programmed cell death 1 (PD-1) monoclonal antibody, have each shown activity as monotherapies for the treatment of renal cell carcinoma.[11,12] As a combination regimen, lenvatinib plus everolimus was shown to be associated with longer progression-free survival than everolimus alone as second-line treatment.[11] In an initial assessment of results from a phase 1b–2 trial, lenvatinib plus pembrolizumab was shown to have promising antitumor activity in previously treated patients with renal cell carcinoma.[13] Here, we report the results of A Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Everolimus or Pembrolizumab versus Sunitinib Alone in First-Line Treatment of Subjects with Advanced Renal Cell Carcinoma (CLEAR).

Methods

Patients

We enrolled patients who were 18 years of age or older and had previously untreated advanced renal cell carcinoma with a clear-cell component and at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Other key inclusion criteria were a Karnofsky performance-status score of at least 70 (scores range from 0 to 100, with lower scores indicating greater disability)[14]; adequately controlled blood pressure, with or without medications; and adequate organ function. Full inclusion and exclusion criteria are described in the protocol, available with the full text of this article at NEJM.org.

Trial Design and Treatment

Patients were randomly assigned in a 1:1:1 ratio to receive treatment with one of three regimens: lenvatinib plus pembrolizumab, lenvatinib plus everolimus, or sunitinib. Randomization was stratified according to geographic region (Western Europe and North America or the rest of the world) and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk group (favorable, intermediate, or poor risk)[15] (definitions are included in the Supplementary Appendix, available at NEJM.org). We report the final analysis of progression-free survival.

In the lenvatinib-plus-pembrolizumab group, lenvatinib was administered at a dose of 20 mg orally once daily for each 21-day treatment cycle, and pembrolizumab was administered at a dose of 200 mg intravenously on day 1 of each 21-day cycle. In the lenvatinib-plus-everolimus group, lenvatinib was administered at a dose of 18 mg and everolimus was administered at a dose of 5 mg orally once daily for each 21-day cycle. Doses for each group were determined on the basis of the results of phase 1 dose-finding trials.[13,16,17] Sunitinib was administered at a dose of 50 mg orally once daily for 4 weeks of treatment followed by 2 weeks with no treatment. Full details regarding the approaches used for dose interruptions and dose reductions can be found in the protocol. Details regarding discontinuation of treatment are provided in the Supplementary Appendix.

Trial Oversight

The trial was conducted in accordance with the International Council for Harmonisation Good Clinical Practice Guidelines and the principles of the 2013 Declaration of Helsinki. Institutional review boards or independent ethics committees approved the protocol and appropriate related documents; all patients provided written informed consent. Safety and efficacy data were monitored by an independent data and safety monitoring committee.

The trial was designed by academic authors and authors who were employees of the sponsors. All the authors had full access to the data and attest to their full participation in the development

and review of the manuscript for publication. The authors vouch for the fidelity of the trial to the protocol and statistical plan and attest to the accuracy and completeness of the data and analyses. A medical writer funded by the sponsors assisted with the preparation of the manuscript.

END POINTS AND ASSESSMENTS

Progression-free survival and all other response-associated end points were assessed with the use of RECIST, version 1.1. The primary end point was progression-free survival as assessed by an independent review committee. Key secondary end points were overall survival and objective response as assessed by an independent review committee. Other secondary end points included safety and progression-free survival as assessed by the investigators. Key exploratory end points included the duration of response as assessed by an independent review committee and objective response as assessed by the investigators. All subgroup analyses were prespecified in the statistical analysis plan. Data on patient-reported outcomes were collected but are not reported here.

Tumor assessments (by computed tomography or magnetic resonance imaging) were performed with the use of RECIST, version 1.1, at screening and every 8 weeks from the date of randomization thereafter. Additional details regarding the frequency of bone and brain scans are provided in the protocol.

For safety assessments, all adverse events and serious adverse events were monitored and recorded with the use of the Common Terminology Criteria for Adverse Events, version 4.03. The adverse events that are summarized and discussed in this report are those that emerged or worsened in severity during treatment (up to 30 days after the last dose of trial drug). Patients also underwent regular monitoring by means of physical examinations and laboratory evaluations for hematologic measures, blood chemical values, and urine values. Vital signs and electrocardiograms were also obtained periodically. Details regarding programmed cell death ligand 1 (PD-L1) testing are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

Sample size was estimated on the basis of the requirements for the progression-free survival analysis, with approximately 1050 patients planned for stratified randomization across groups. The same treatment effect was assumed for the primary comparisons of lenvatinib plus pembrolizumab and lenvatinib plus everolimus with sunitinib. Assumptions of a median progression-free survival of 12.3 months with sunitinib and a hazard ratio for disease progression or death of 0.714 in evaluations of each drug combination as compared with sunitinib would correspond to 40% longer median progression-free survival (i.e., 17.2 months) with each of the two drug combinations. We calculated that power of 90% with a two-sided alpha of 0.045 would be achieved with 388 events of disease progression or death between the lenvatinib-plus-pembrolizumab and sunitinib groups; the power for evaluating lenvatinib plus everolimus as compared with sunitinib at an alpha of 0.0049 was 70%, which would be at least 90% after alpha reallocation from previous rejected tests. Details regarding prespecified interim analyses of progression-free survival, overall survival, and objective response are provided in the Supplementary Appendix.

A sequential approach[18] for multiple comparisons was used to adjust for multiplicity and to control the familywise error rate for progression-free survival and overall survival and the percentage of patients with an objective response at the alpha of 0.0499 (two-sided) in comparisons of each combination regimen with sunitinib. All stratified analyses applied the stratification factors used at randomization.

Efficacy was assessed in the intention-to-treat population, which included all the patients who underwent randomization. Progression-free survival and overall survival were evaluated with Kaplan–Meier estimates and two-sided 95% confidence intervals. Differences between each combination regimen and sunitinib were evaluated with the stratified log-rank test. A stratified Cox regression model with Efron's method for handling tied results was used to estimate the hazard ratios and 95% confidence intervals. Between-group differences in the percentage of patients with an objective response were evaluated with a stratified Cochran–Mantel–Haenszel test; the stratified relative risk and 95% confidence intervals are provided. The duration of response in patients with a confirmed response was estimated by the Kaplan–Meier method.

Safety analyses included all the patients who received at least one dose of any trial drug. The full statistical analysis plan is available with the protocol.

RESULTS

PATIENTS AND TREATMENTS

Between October 13, 2016, and July 24, 2019, a total of 1417 patients were screened for eligibility, 1069 of whom underwent randomization: 355 were assigned to receive lenvatinib plus pembrolizumab, 357 to receive lenvatinib plus everolimus, and 357 to receive sunitinib (Fig. S1 in the Supplementary Appendix). The trial involved 200 sites in 20 countries.

Baseline demographic and disease characteristics of the patients were balanced among the treatment groups (Table 1). Data cutoff occurred on August 28, 2020, for the final analysis of progression-free survival, with a median follow-up for overall survival of 26.6 months. At the cutoff date, treatment was ongoing for 40.0% of the patients in the lenvatinib-plus-pembrolizumab group, 31.4% of the patients in the lenvatinib-plus-everolimus group, and 18.8% of the patients in the sunitinib group. The primary reason for treatment discontinuation in any group was disease progression.

Among patients who discontinued therapy, 54.9% in the lenvatinib-plus-pembrolizumab group, 68.2% in the lenvatinib-plus-everolimus group, and 71.0% in the sunitinib group received subsequent systemic therapy during follow-up (Table S1 in the Supplementary Appendix). Antiangiogenic therapy was the most common therapy received after treatment with lenvatinib plus pembrolizumab (in 50.7% of patients), whereas PD-1–PD-L1 checkpoint inhibitor therapy was the most commonly received therapy after lenvatinib plus everolimus (51.4%) or sunitinib (53.1%).

EFFICACY

Progression-free survival as determined by an independent review committee was significantly longer in the lenvatinib-plus-pembrolizumab group than in the sunitinib group (median, 23.9 months [95% confidence interval {CI}, 20.8 to 27.7] vs. 9.2 months [95% CI, 6.0 to 11.0]; hazard ratio for disease progression or death, 0.39; 95% CI, 0.32 to 0.49; P<0.001) and was significantly longer in the lenvatinib-plus-everolimus group than in the sunitinib group (median, 14.7 months [95% CI, 11.1 to 16.7] vs. 9.2 months [95% CI, 6.0 to 11.0]; hazard ratio, 0.65; 95% CI, 0.53 to 0.80; P<0.001) (Fig. 1A). Progression-free survival as assessed by the investigators was also longer with lenvatinib plus pembrolizumab than with sunitinib (median, 22.1 months [95% CI, 17.1 to 26.9] vs. 9.5 months [95% CI, 7.9 to 11.1]; hazard ratio, 0.47; 95% CI, 0.38 to 0.58) and longer with lenvatinib plus everolimus than with sunitinib (median, 14.6 months [95% CI, 11.2 to 18.0] vs. 9.5 months [95% CI, 7.9 to 11.1]; hazard ratio, 0.70; 95% CI, 0.57 to 0.85) (Fig. S2). The results for progression-free survival favored the two combination regimens over sunitinib across all evaluated subgroups, including those based on MSKCC prognostic risk group and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk group (Figs. 1B and S3).

In the analysis of overall survival, 79.2% of the patients in the lenvatinib-plus-pembrolizumab group, 66.1% of the patients in the lenvatinib-plus-everolimus group, and 70.4% of the patients in the sunitinib group were alive at 24 months. Median overall survival was not reached with any treatment; survival was significantly longer with lenvatinib plus pembrolizumab than with sunitinib (hazard ratio for death, 0.66; 95% CI, 0.49 to 0.88; P=0.005) (Fig. 2A). Overall survival with lenvatinib plus everolimus was not significantly longer than that with sunitinib (hazard ratio, 1.15; 95% CI, 0.88 to 1.50; P=0.30) (Fig. 2A). Subgroup analyses of overall survival according to baseline characteristics are shown in Fig. S4. The hazard ratio for overall survival favored lenvatinib plus pembrolizumab over sunitinib in most subgroups, including patients with PD-L1–positive or –negative tumors, with an exception observed in patients with favorable risk features as defined by IMDC criteria.

The percentage of patients with a confirmed objective response to treatment as determined by an independent review committee with the use of RECIST, version 1.1, was 71.0% with lenvatinib plus pembrolizumab, 53.5% with lenvatinib plus everolimus, and 36.1% with sunitinib (relative risk with lenvatinib plus pembrolizumab vs. sunitinib, 1.97 [95% CI, 1.69 to 2.29]; and

Table 1. Demographic and Clinical Characteristics at Baseline.*

Characteristic	Lenvatinib plus Pembrolizumab (N=355)	Lenvatinib plus Everolimus (N=357)	Sunitinib (N=357)
Median age (range) — yr	64 (34–88)	62 (32–86)	61 (29–82)
Age <65 yr — no. (%)	194 (54.6)	201 (56.3)	225 (63.0)
Sex — no. (%)			
Male	255 (71.8)	266 (74.5)	275 (77.0)
Female	100 (28.2)	91 (25.5)	82 (23.0)
Geographic region — no. (%)			
Western Europe or North America	198 (55.8)	200 (56.0)	199 (55.7)
Rest of the world	157 (44.2)	157 (44.0)	158 (44.3)
Karnofsky performance-status score — no. (%)†			
100–90	295 (83.1)	286 (80.1)	294 (82.4)
80–70	60 (16.9)	70 (19.6)	62 (17.4)
MSKCC prognostic risk group — no. (%)‡			
Favorable	96 (27.0)	98 (27.5)	97 (27.2)
Intermediate	227 (63.9)	227 (63.6)	228 (63.9)
Poor	32 (9.0)	32 (9.0)	32 (9.0)
IMDC prognostic risk group — no. (%)§			
Favorable	110 (31.0)	114 (31.9)	124 (34.7)
Intermediate	210 (59.2)	195 (54.6)	192 (53.8)
Poor	33 (9.3)	42 (11.8)	37 (10.4)
Could not be evaluated	2 (0.6)	6 (1.7)	4 (1.1)
Sarcomatoid features — no. (%)	28 (7.9)	24 (6.7)	21 (5.9)
PD-L1 combined positive score — no. (%)¶			
≥1	107 (30.1)	116 (32.5)	119 (33.3)
<1	112 (31.5)	118 (33.1)	103 (28.9)
Not available	136 (38.3)	123 (34.5)	135 (37.8)
No. of metastatic organs or sites — no. (%)‖			
1	97 (27.3)	125 (35.0)	108 (30.3)
≥2	254 (71.5)	229 (64.1)	246 (68.9)
Site of metastasis — no. (%)**			
Lung	249 (70.1)	245 (68.6)	239 (66.9)
Lymph node	170 (47.9)	163 (45.7)	159 (44.5)
Bone	85 (23.9)	86 (24.1)	97 (27.2)
Liver	60 (16.9)	62 (17.4)	61 (17.1)
Previous nephrectomy — no. (%)	262 (73.8)	260 (72.8)	275 (77.0)

* Percentages may not total 100 because of rounding. One patient in the lenvatinib-plus-pembrolizumab group had carcinoma without a clear-cell component.

† Karnofsky performance-status scores range from 0 to 100, with lower scores indicating greater disability. Scores were missing for 1 patient each in the lenvatinib-plus-everolimus and sunitinib groups.

‡ A Memorial Sloan Kettering Cancer Center (MSKCC) score of 0 indicates favorable risk, a score of 1 or 2 intermediate risk, and a score of 3 or higher poor risk. MSKCC scores are defined in the Supplementary Appendix.

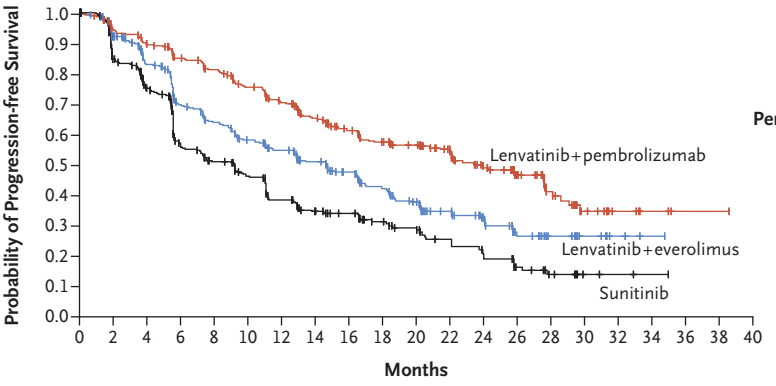
§ An International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) score of 0 indicates favorable risk, a score of 1 or 2 intermediate risk, and a score of 3 to 6 poor risk. IMDC scores are defined in the Supplementary Appendix.

¶ Programmed cell death ligand 1 (PD-L1) expression was assessed with the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies) and reported as the combined positive score, defined as the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100.

‖ Kidney was not included in the number of metastatic organs or sites. The only tumor location was in the kidney for 3 patients (0.8%) in the lenvatinib-plus-everolimus group, 4 patients (1.1%) in the lenvatinib-plus-pembrolizumab group, and 3 patients (0.8%) in the sunitinib group.

** Four common sites of metastasis are shown. Patients may have had metastasis at more than one site.

A Kaplan–Meier Analysis of Progression-free Survival



Median Progression-free Survival (95% CI)	*mo*
Lenvatinib+ Pembrolizumab	23.9 (20.8–27.7)
Lenvatinib+ Everolimus	14.7 (11.1–16.7)
Sunitinib	9.2 (6.0–11.0)

Hazard ratio for disease progression or death (lenvatinib+pembrolizumab vs. sunitinib), 0.39 (95% CI, 0.32–0.49); P<0.001

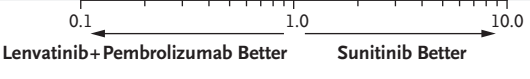
Hazard ratio for disease progression or death (lenvatinib+everolimus vs. sunitinib), 0.65 (95% CI, 0.53–0.80); P<0.001

No. at Risk

Lenvatinib+pembrolizumab	355	321	300	276	259	235	213	186	160	136	126	106	80	56	30	14	6	3	1	1	0
Lenvatinib+everolimus	357	305	259	207	185	163	149	125	105	85	70	53	37	20	13	7	3	1	0		
Sunitinib	357	262	218	145	124	107	85	69	62	49	42	32	25	16	9	3	2	1	0		

B Subgroup Analysis of Progression-free Survival

Subgroup	Lenvatinib+ Pembrolizumab	Sunitinib	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of events/no. of patients		
Overall	160/355	205/357	0.39 (0.32–0.49)
Age			
<65 yr	88/194	134/225	0.37 (0.28–0.49)
≥65 yr	72/161	71/132	0.43 (0.31–0.61)
Sex			
Male	120/255	158/275	0.38 (0.30–0.49)
Female	40/100	47/82	0.42 (0.27–0.66)
Geographic region			
Western Europe and North America	86/198	108/199	0.42 (0.32–0.57)
Rest of the world	74/157	97/158	0.36 (0.26–0.49)
MSKCC risk group			
Favorable	39/96	60/97	0.36 (0.23–0.54)
Intermediate	101/227	126/228	0.44 (0.34–0.58)
Poor	20/32	19/32	0.18 (0.08–0.42)
IMDC risk group			
Favorable	43/110	67/124	0.41 (0.28–0.62)
Intermediate	97/210	110/192	0.39 (0.29–0.52)
Poor	18/33	26/37	0.28 (0.13–0.60)
Baseline Karnofsky performance-status score			
100–90	125/295	172/294	0.38 (0.30–0.48)
80–70	35/60	33/62	0.44 (0.26–0.74)
No. of organs with metastases			
1	39/97	54/108	0.46 (0.30–0.71)
≥2	120/254	150/246	0.36 (0.28–0.47)
PD-L1 combined positive score			
≥1	51/107	78/119	0.40 (0.27–0.58)
<1	48/112	58/103	0.39 (0.26–0.59)



with lenvatinib plus everolimus vs. sunitinib, 1.48 [95% CI, 1.26 to 1.74]) (Table 2). The percentage of patients with a complete response was 16.1% in the lenvatinib-plus-pembrolizumab group, 9.8% in the lenvatinib-plus-everolimus group, and 4.2% in the sunitinib group (Table 2). The median duration of response in patients who had a confirmed response was 25.8 months

Figure 1 (facing page). Progression-free Survival.
Panel A shows the Kaplan–Meier curves for progression-free survival in each treatment group. Tick marks indicate censored data. Panel B shows the analysis of progression-free survival in subgroups of patients in the lenvatinib-plus-pembrolizumab group and the sunitinib group. Progression-free survival was assessed according to Response Evaluation Criteria in Solid Tumors, version 1.1, by an independent review committee. Differences between the treatment groups were evaluated with the stratified log-rank test, stratified according to geographic region and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic risk group. A stratified Cox regression model was used to estimate the hazard ratio for disease progression or death and 95% confidence intervals (CIs). MSKCC and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk groups are defined in the Supplementary Appendix. Karnofsky performance-status scores range from 0 to 100, with lower scores indicating greater disability. The programmed cell death ligand 1 (PD-L1) combined positive score is defined as the number of PD-L1–staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100.

(95% CI, 22.1 to 27.9) in the lenvatinib-plus-pembrolizumab group, 16.6 months (95% CI, 14.6 to 20.6) in the lenvatinib-plus-everolimus group, and 14.6 months (95% CI, 9.4 to 16.7) in the sunitinib group (Table 2 and Fig. 2B). The results for objective response as assessed by the investigators was consistent with those for objective response as assessed by the independent review committee (Table S2).

EXPOSURE AND SAFETY

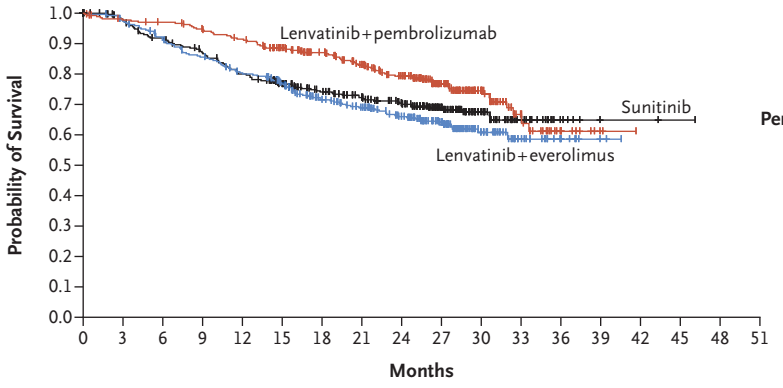
The median duration of treatment was 17.0 months (range, 0.1 to 39.1) in the lenvatinib-plus-pembrolizumab group, 11.0 months (range, 0.1 to 40.0) in the lenvatinib-plus-everolimus group, and 7.8 months (range, 0.1 to 37.0) in the sunitinib group. The median relative dose intensity of lenvatinib per patient was 69.6% (range, 12.6 to 157.1) in the lenvatinib-plus-pembrolizumab group and 70.4% (range, 22.9 to 100.0) in the lenvatinib-plus-everolimus group. The median relative dose intensity of everolimus per patient was 89.3% (range, 27.6 to 100.0) in the lenvatinib-plus-everolimus group. The median number of infusions of pembrolizumab per patient was 22 (range, 1 to 39). The median relative dose intensity of sunitinib was 83.2% (range, 18.8 to 100.0).

Almost all patients in each group had adverse events (of any cause) that emerged or worsened during treatment (99.7% of the patients in both the lenvatinib-plus-pembrolizumab group and the lenvatinib-plus-everolimus group and 98.5% of the patients in the sunitinib group), with diarrhea being the most common event in each group (in 61.4% of the patients in the lenvatinib-plus-pembrolizumab group, in 66.5% of those in the lenvatinib-plus-everolimus group, and in 49.4% of those in the sunitinib group) (Tables 3 and S3). Grade 3 or higher adverse events of any cause occurred in 82.4% of the patients who received lenvatinib plus pembrolizumab, in 83.1% of the patients who received lenvatinib plus everolimus, and in 71.8% of the patients who received sunitinib. Grade 3 or higher adverse events that occurred in 10% or more of patients in any treatment group included diarrhea, hypertension, an elevated lipase level, and hypertriglyceridemia.

In the lenvatinib-plus-pembrolizumab group, adverse events of any grade led to discontinuation of lenvatinib, pembrolizumab, or both drugs in 37.2% of patients (lenvatinib, 25.6%; pembrolizumab, 28.7%; both drugs, 13.4%); led to dose reduction of lenvatinib in 68.8% of patients; and led to interruption of lenvatinib, pembrolizumab, or both drugs in 78.4% of patients. In the lenvatinib-plus-everolimus group, adverse events of any grade led to discontinuation of lenvatinib, everolimus, or both drugs in 27.0% of patients (lenvatinib, 22.0%; everolimus, 24.8%; both drugs, 18.9%); led to dose reduction of lenvatinib, everolimus, or both drugs in 73.2% patients; and led to interruption of lenvatinib, everolimus, or both drugs in 83.4% of patients. In the sunitinib group, adverse events of any grade led to discontinuation of sunitinib in 14.4% patients, led to dose reduction in 50.3% patients, and led to treatment interruption in 53.8% patients. The median time to discontinuation due to adverse events was 8.97 months in the lenvatinib-plus-pembrolizumab group, 5.49 months in the lenvatinib-plus-everolimus group, and 4.57 months in the sunitinib group.

Adverse events that were frequently judged by the investigators to be related to the trial treatment across the treatment groups included diarrhea and hypertension (Table S4). Adverse events of interest that were associated with pembrolizumab and everolimus, as well as clinically sig-

A Kaplan–Meier Analysis of Overall Survival



Median Overall Survival (95% CI)	*mo*
Lenvatinib+ Pembrolizumab	NR (33.6–NE)
Lenvatinib+ Everolimus	NR (NE–NE)
Sunitinib	NR (NE–NE)

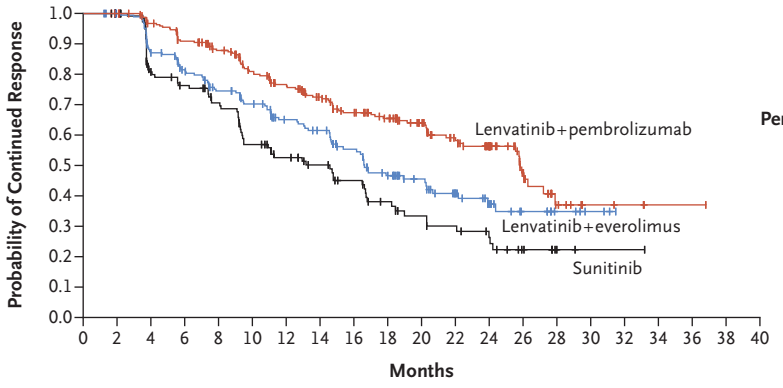
Hazard ratio for death (lenvatinib+ pembrolizumab vs. sunitinib), 0.66 (95% CI, 0.49–0.88); P=0.005

Hazard ratio for death (lenvatinib+ everolimus vs. sunitinib), 1.15 (95% CI, 0.88–1.50); P=0.30

No. at Risk

Lenvatinib+pembrolizumab	355	342	338	327	313	280	253	222	188	129	66	26	10	2	0			
Lenvatinib+everolimus	357	346	321	299	277	246	205	183	154	109	46	22	8	2	0			
Sunitinib	357	332	307	289	264	236	207	186	160	112	60	25	7	2	2	1	0	

B Kaplan–Meier Analysis of Response Duration



Median Duration of Response (95% CI)	*mo*
Lenvatinib+ Pembrolizumab	25.8 (22.1–27.9)
Lenvatinib+ Everolimus	16.6 (14.6–20.6)
Sunitinib	14.6 (9.4–16.7)

No. at Risk

Lenvatinib+pembrolizumab	252	250	234	215	197	172	153	131	112	101	83	63	45	23	9	4	3	1	1	0
Lenvatinib+everolimus	191	186	159	142	125	113	93	83	65	50	39	27	18	11	6	3	0			
Sunitinib	129	125	91	82	73	57	47	40	33	25	20	17	13	7	2	1	1	0		

Figure 2. Overall Survival and Duration of Response.

Panel A shows the Kaplan–Meier curves for overall survival, and Panel B shows the Kaplan–Meier curves for the duration of response in patients who had a response. Tick marks indicate censored data. NE denotes could not be estimated, and NR not reached.

nificant adverse events that emerged or worsened during treatment with lenvatinib, are described in Tables S5 through S7.

DISCUSSION

In this phase 3 trial involving patients with advanced renal cell carcinoma, we evaluated two regimens as first-line treatment — lenvatinib plus pembrolizumab and lenvatinib plus everolimus — as compared with the standard of care, sunitinib. Progression-free survival, the primary end point, was significantly longer among patients treated with either lenvatinib plus pembrolizumab or lenvatinib plus everolimus than among those treated with sunitinib. Treatment with lenvatinib plus pembrolizumab was also associated with significantly longer overall survival than sunitinib. However, treatment with lenvatinib plus everolimus did not have a significantly greater effect on overall survival than sunitinib. The efficacy outcomes as evaluated by

Table 2. Confirmed Tumor Responses.*

Measure	Lenvatinib plus Pembrolizumab (N=355)	Lenvatinib plus Everolimus (N=357)	Sunitinib (N=357)
Objective response (95% CI) — %†	71.0 (66.3–75.7)	53.5 (48.3–58.7)	36.1 (31.2–41.1)
Relative risk vs. sunitinib (95% CI)	1.97 (1.69–2.29)	1.48 (1.26–1.74)	Reference
Best overall response — no. (%)			
Complete response	57 (16.1)	35 (9.8)	15 (4.2)
Partial response	195 (54.9)	156 (43.7)	114 (31.9)
Stable disease	68 (19.2)	120 (33.6)	136 (38.1)
Progressive disease	19 (5.4)	26 (7.3)	50 (14.0)
Unknown or could not be evaluated‡	16 (4.5)	20 (5.6)	42 (11.8)
Median time to response (range) — mo	1.94 (1.41–18.50)	1.91 (1.41–14.36)	1.94 (1.61–16.62)
Median duration of response (95% CI) — mo	25.8 (22.1–27.9)	16.6 (14.6–20.6)	14.6 (9.4–16.7)

* Responses were assessed by an independent review committee with Response Evaluation Criteria in Solid Tumors, version 1.1. Percentages may not total 100 due to rounding.
† Additional details of the statistical analysis and the results of interim analysis 2 (a prespecified interim analysis that had been planned as the final analysis of objective response) are provided in the Supplementary Appendix.
‡ The best overall response was unknown or could not be evaluated for patients who had no baseline or no postbaseline tumor assessments, at least one lesion that could not be evaluated, or early stable disease (occurring <7 weeks after randomization).

the independent review committee were consistent with those evaluated by the investigators, across all therapies. Moreover, the results for progression-free and overall survival favored lenvatinib plus pembrolizumab over sunitinib in most evaluated subgroups.

The safety profile of each combination therapy was consistent with that of each component as a single agent, as well as with the previously reported safety profiles for each combination.[11,13,17,19-21] Adverse events that emerged or worsened during treatment resulted in dose reduction of lenvatinib in 68.8% of patients in the lenvatinib-plus-pembrolizumab group and dose reduction of lenvatinib, everolimus, or both drugs in 73.2% of patients in the lenvatinib-plus-everolimus group. Interruption or dose reduction of lenvatinib after initiation of treatment is a common strategy (irrespective of indication) to maximize therapeutic benefit while reducing the risk of toxic effects. Overall, interruptions and reductions were effectively used in this trial, which allowed patients to continue to receive life-prolonging therapy for a longer period. Although the combination of lenvatinib and pembrolizumab was associated with some notable side effects, these adverse events are often adequately managed with medical therapy if they are diagnosed early during patient visits. Of note, adverse events associated with lenvatinib plus pembrolizumab were likely to have been influenced by the longer treatment duration in this group than in the sunitinib group.

Although caution should be used when comparing trials, in this trial, the median progression-free survival in the lenvatinib-plus-pembrolizumab group (23.9 months), along with the percentage of patients in that group who had an objective response (71.0%) — and especially the 16.1% of patients who had a complete response — were notable relative to findings in other pivotal first-line trials in advanced renal cell carcinoma, including recent trials of immune-checkpoint inhibitor–containing regimens.[3-6,22] Moreover, the percentage of patients alive at 24 months in the lenvatinib-plus-pembrolizumab group (79.2%) was noteworthy in the context of other immune-checkpoint inhibitor–containing regimens.[3-6,22]

Progression-free survival was significantly longer with lenvatinib plus everolimus than with sunitinib; however, only lenvatinib plus pembrolizumab showed a benefit for overall survival as compared with sunitinib. The finding of an overall survival benefit of lenvatinib in combination

Table 3. Adverse Events of Any Cause That Emerged or Worsened during Treatment in at Least 25% of the Patients in Any Treatment Group.*

Event	Lenvatinib plus Pembrolizumab (N=352)		Lenvatinib plus Everolimus (N=355)		Sunitinib (N=340)	
	Any Grade	Grade ≥3†	Any Grade	Grade ≥3†	Any Grade	Grade ≥3†
	number of patients (percent)					
Any event	351 (99.7)	290 (82.4)	354 (99.7)	295 (83.1)	335 (98.5)	244 (71.8)
Diarrhea	216 (61.4)	34 (9.7)	236 (66.5)	41 (11.5)	168 (49.4)	18 (5.3)
Hypertension	195 (55.4)	97 (27.6)	162 (45.6)	80 (22.5)	141 (41.5)	64 (18.8)
Hypothyroidism‡	166 (47.2)	5 (1.4)	95 (26.8)	2 (0.6)	90 (26.5)	0
Decreased appetite	142 (40.3)	14 (4.0)	144 (40.6)	22 (6.2)	105 (30.9)	5 (1.5)
Fatigue	141 (40.1)	15 (4.3)	149 (42.0)	27 (7.6)	125 (36.8)	15 (4.4)
Nausea	126 (35.8)	9 (2.6)	141 (39.7)	9 (2.5)	113 (33.2)	2 (0.6)
Stomatitis	122 (34.7)	6 (1.7)	169 (47.6)	22 (6.2)	131 (38.5)	7 (2.1)
Dysphonia	105 (29.8)	0	84 (23.7)	2 (0.6)	14 (4.1)	0
Weight decrease	105 (29.8)	28 (8.0)	116 (32.7)	26 (7.3)	31 (9.1)	1 (0.3)
Proteinuria	104 (29.5)	27 (7.7)	121 (34.1)	29 (8.2)	43 (12.6)	10 (2.9)
Palmar–plantar erythrodysesthesia syndrome	101 (28.7)	14 (4.0)	81 (22.8)	10 (2.8)	127 (37.4)	13 (3.8)
Arthralgia	99 (28.1)	5 (1.4)	76 (21.4)	5 (1.4)	52 (15.3)	1 (0.3)
Rash	96 (27.3)	13 (3.7)	88 (24.8)	1 (0.3)	47 (13.8)	2 (0.6)
Vomiting	92 (26.1)	12 (3.4)	113 (31.8)	10 (2.8)	68 (20.0)	5 (1.5)
Constipation	89 (25.3)	3 (0.9)	73 (20.6)	1 (0.3)	64 (18.8)	0
Dysgeusia	43 (12.2)	1 (0.3)	59 (16.6)	0	95 (27.9)	1 (0.3)

* Safety assessments were based on as-treated principle and consisted of monitoring and recording all adverse events and serious adverse events with the use of the Common Terminology Criteria for Adverse Events, version 4.03, in the group of patients who received at least one dose of trial drug. Events are listed in descending order of frequency in the lenvatinib-plus-pembrolizumab group. Adverse events were coded to the *Medical Dictionary for Regulatory Activities*, version 21.1 or higher, lower-level term closest to the verbatim term.

† Of the 15 patients in the lenvatinib-plus-pembrolizumab group who had grade 5 adverse events during treatment, 11 had fatal events not attributed to disease progression (acute renal failure, uncontrolled hypertension, complications from myasthenic syndrome, complications from autoimmune hepatitis, cardiac arrest, and death–cause not specified in 1 patient each; hemorrhagic events in 2 patients; and sepsis in 3 patients). In the lenvatinib-plus-everolimus group, of the 22 patients with grade 5 adverse events, 10 had fatal events not attributed to disease progression (pneumonia, urosepsis, colon perforation, fistula, infection, and pneumothorax in 1 patient each; hemorrhagic events and death–cause not specified in 2 patients each). Among the 11 patients in the sunitinib group with grade 5 adverse events during treatment, fatal events not attributed to disease progression occurred in 2 patients (respiratory failure and acute kidney injury in 1 patient and death–cause not specified in 1 patient).

‡ Hypothyroidism is an adverse event of interest associated with pembrolizumab; additional information regarding adverse events of interest is provided in the Supplementary Appendix. Information regarding these adverse events was not collected specifically as "immune-related," in order to preserve blinding.

with pembrolizumab but not in combination with everolimus confirms that an immune-checkpoint inhibitor–kinase inhibitor combination therapy is important in the first-line treatment of patients with advanced renal cell carcinoma.

A limitation of this trial was that patients and investigators were aware of the treatment-group assignments. In addition, different percentages of patients with known prognostic risk features, including poor IMDC risk and sarcomatoid histologic features, should be considered in cross-trial comparisons. Although data on patient-reported outcomes were collected, the analysis is not yet available. Longer follow-up in this trial would also help to better define the long-term efficacy of these combination regimens.

Our trial showed that combination therapy with lenvatinib plus pembrolizumab provided significantly greater benefits than sunitinib with regard to progression-free survival and overall sur-

vival in the first-line treatment of patients with advanced renal cell carcinoma. Grade 3 or higher adverse events occurring in 10% or more of patients in any group included hypertension, diarrhea, and generally asymptomatic elevations in lipase levels. The safety profile of lenvatinib plus pembrolizumab was consistent with the known profile of each drug.

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APPENDIX

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