

ORIGINAL ARTICLE

Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer

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ABSTRACT

BACKGROUND

Standard therapy for advanced endometrial cancer after failure of platinum-based chemotherapy remains unclear.

METHODS

In this phase 3 trial, we randomly assigned, in a 1:1 ratio, patients with advanced endometrial cancer who had previously received at least one platinum-based chemotherapy regimen to receive either lenvatinib (20 mg, administered orally once daily) plus pembrolizumab (200 mg, administered intravenously every 3 weeks) or chemotherapy of the treating physician's choice (doxorubicin at 60 mg per square meter of body-surface area, administered intravenously every 3 weeks, or paclitaxel at 80 mg per square meter, administered intravenously weekly [with a cycle of 3 weeks on and 1 week off]). The two primary end points were progression-free survival as assessed on blinded independent central review according to the Response Evaluation Criteria in Solid Tumors, version 1.1, and overall survival. The end points were evaluated in patients with mismatch repair–proficient (pMMR) disease and in all patients. Safety was also assessed.

RESULTS

A total of 827 patients (697 with pMMR disease and 130 with mismatch repair–deficient disease) were randomly assigned to receive lenvatinib plus pembrolizumab (411 patients) or chemotherapy (416 patients). The median progression-free survival was longer with lenvatinib plus pembrolizumab than with chemotherapy (pMMR population: 6.6 vs. 3.8 months; hazard ratio for progression or death, 0.60; 95% confidence interval [CI], 0.50 to 0.72; $P < 0.001$; overall: 7.2 vs. 3.8 months; hazard ratio, 0.56; 95% CI, 0.47 to 0.66; $P < 0.001$). The median overall survival was longer with lenvatinib plus pembrolizumab than with chemotherapy (pMMR population: 17.4 vs. 12.0 months; hazard ratio for death, 0.68; 95% CI, 0.56 to 0.84; $P < 0.001$; overall: 18.3 vs. 11.4 months; hazard ratio, 0.62; 95% CI, 0.51 to 0.75; $P < 0.001$). Adverse events of grade 3 or higher occurred in 88.9% of the patients who received lenvatinib plus pembrolizumab and in 72.7% of those who received chemotherapy.

CONCLUSIONS

Lenvatinib plus pembrolizumab led to significantly longer progression-free survival and overall survival than chemotherapy among patients with advanced endometrial cancer. (Funded by Eisai and Merck Sharp and Dohme [a subsidiary of Merck]; Study 309–KEYNOTE-775 ClinicalTrials.gov number, NCT03517449.)

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*A list of the Study 309–KEYNOTE-775 investigators is provided in the Supplementary Appendix, available at NEJM.org.

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METHODS

PATIENTS

We enrolled women 18 years of age or older with confirmed advanced, recurrent, or metastatic endometrial cancer of any histologic subtype, except carcinosarcoma and sarcoma. Eligible women had disease progression after the receipt of one previous platinum-based chemotherapy regimen, with no history of exposure to vascular endothelial growth factor- or PD-1-targeting regimens. Patients may have received two lines of platinum-based chemotherapy if one was given as neoadjuvant or adjuvant therapy. There was no restriction regarding the previous receipt of hormonal therapy. Other inclusion criteria were the following: at least one measurable lesion according to RECIST, version 1.1; available biopsy specimens for the determination of MMR status; and an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 (on a 5-point scale, with higher scores indicating greater disability). The full lists of the inclusion and exclusion criteria are provided in the protocol, available with the full text of this article at NEJM.org.

TRIAL DESIGN AND TREATMENTS

This multicenter, open-label, phase 3 trial had a screening phase of up to 28 days, after which eligible patients were randomly assigned (in a 1:1 ratio) to receive either lenvatinib plus pembrolizumab or chemotherapy of the treating physician's choice (with doxorubicin or paclitaxel chosen before randomization; chemotherapy group). In the lenvatinib-pembrolizumab group, patients received lenvatinib at a dose of 20 mg, administered orally once daily, plus pembrolizumab at a dose of 200 mg, administered intravenously as a 30-minute infusion every 3 weeks, on the basis of previous dose-finding studies.²⁶ Patients could have received up to 35 doses of pembrolizumab in the trial. In the chemotherapy group, patients received doxorubicin at a dose of 60 mg per square meter of body-surface area, administered intravenously as a 1-hour infusion or according to institutional guidelines, every 3 weeks, or paclitaxel at a dose of 80 mg per square meter, administered intravenously as a 1-hour infusion or according to institutional guidelines, weekly (with a cycle of 3 weeks on and 1 week off). Randomization to treatment group was initially

THE INCIDENCE OF ENDOMETRIAL CANCER is increasing worldwide.¹⁻⁴ Approximately 10 to 15% of patients with endometrial cancer present with advanced-stage disease,⁵ and 5-year survival among patients with distant metastases has been reported to be 17%.⁶ No treatments have been globally accepted as the standard of care for advanced or recurrent endometrial cancer after the failure of platinum-based chemotherapy.^{7,8} Targeted therapies and chemotherapy have had limited efficacy, substantial toxic effects, or both.⁹⁻¹⁶ Lenvatinib, a multitargeted tyrosine kinase inhibitor of vascular endothelial growth factor receptors 1 through 3, fibroblast growth factor receptors 1 through 4, platelet-derived growth factor receptor α , RET, and KIT,¹⁷ has limited efficacy as second-line treatment for recurrent endometrial carcinoma (objective response in 14.3% [95% confidence interval {CI}, 8.8 to 21.4] of patients, as assessed on independent review according to Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1).¹⁸ In a nonrandomized study, checkpoint inhibitors, including pembrolizumab (a programmed cell death 1 [PD-1] inhibitor), had compelling antitumor activity, as assessed on the basis of objective response and duration of response, in patients with microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) advanced endometrial carcinoma.¹⁹ However, only 16 to 31% of endometrial cancers are MSI-H or dMMR.²⁰⁻²³ Furthermore, pembrolizumab monotherapy has shown less activity in patients with microsatellite-stable or mismatch repair-proficient (pMMR) disease than in those with MSI-H or dMMR disease.^{19,24}

In the Study 111-KEYNOTE-146 trial,²⁵ treatment with lenvatinib in combination with pembrolizumab had compelling efficacy in patients with previously treated advanced endometrial carcinoma; high-grade adverse events were managed with supportive therapy and dose modifications, with a relatively low incidence of discontinuation due to adverse events. We conducted the Study 309-KEYNOTE-775 trial to confirm the results of the earlier trial by comparing the efficacy and safety of lenvatinib plus pembrolizumab with the physician's choice of doxorubicin or paclitaxel chemotherapy in patients with advanced endometrial cancer who had disease progression after the receipt of at least one platinum-based therapy.

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stratified according to MMR status (deficient [dMMR] or proficient [pMMR]). Furthermore, within the pMMR population, patients were stratified according to ECOG performance-status score (0 or 1), geographic region (region 1 [Australia, Canada, Europe, Israel, New Zealand, and the United States] or region 2 [rest of the world]), and history of pelvic irradiation (yes or no). Details regarding treatment duration, discontinuation, and dose modifications are provided in the Supplementary Appendix, available at NEJM.org.

TRIAL OVERSIGHT

The trial was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation and ethical principles originating from the Declaration of Helsinki. All the patients provided written informed consent. Institutional review boards or independent ethics committees approved the trial protocol at each site. Data from the interim analysis were collected by the investigator, monitored by an external data and safety monitoring committee, and analyzed by independent central reviewers. The trial was designed by academic authors and employees of the sponsors (Eisai and Merck Sharp and Dohme [a subsidiary of Merck]). All the authors had full access to the data and attest to their participation in the preparation and review of the manuscript. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. A medical writer, funded by the sponsors, assisted with the preparation of an earlier version of the manuscript.

END POINTS

The two primary end points were progression-free survival as assessed on blinded independent central review according to RECIST, version 1.1, and overall survival. Secondary end points included objective response as assessed on blinded independent central review according to RECIST, version 1.1; safety and side-effect profile; and health-related quality of life (assessed with the use of the global health status and quality-of-life score of the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire–Core 30 [QLQ-C30]); and the exposure–safety relationship of lenvatinib therapy. A full list of the secondary end points is available

in the protocol. Duration of response was an exploratory end point.

All the end points were assessed in the pMMR population and among all patients. Subgroup analyses were prespecified. Details regarding tumor assessments are provided in the Supplementary Methods section. Adverse events occurring from the time of treatment assignment until 30 days after treatment discontinuation were recorded and were graded according to the Common Terminology Criteria for Adverse Events, version 4.03, of the National Cancer Institute.

STATISTICAL ANALYSIS

The planned sample was approximately 780 patients (with 660 patients in the pMMR population and 120 in the dMMR population). The first interim analysis was the final efficacy analysis for progression-free survival and an interim efficacy analysis for overall survival. This analysis was to be conducted at least 6 months after the last patient had undergone randomization and when approximately 368 deaths had occurred in the pMMR population. Sample-size and power calculations for the analysis of overall survival were based on the pMMR population. We calculated that with 660 patients in the pMMR population, a total of 526 deaths would provide the trial with 90% power to detect a significant difference at the 0.049 level in the final analysis of overall survival, under the assumptions that the hazard ratio for death would be 0.75, that the first and second interim analyses would be performed when approximately 368 and 463 deaths, respectively, had occurred; and that a Lan–DeMets spending function with the O’Brien–Fleming boundary would be used. For the analysis of progression-free survival, we estimated that 564 events of progression or death would provide the trial with more than 99% power to detect a significant difference at the 0.001 level, under the assumption that the hazard ratio for progression or death would be 0.55. Primary efficacy analyses were conducted in the intention-to-treat population (defined as all the patients who underwent randomization).

Treatment differences in the analyses of progression-free survival and overall survival were assessed by means of the stratified log-rank test (with two-sided P values); the nonparametric Kaplan–Meier method was used to estimate curves. A stratified Cox proportional-hazards

model with Efron's method of tie handling was used to assess hazard ratios. The stratified Miettinen and Nurminen's method was used to determine between-group differences in objective response. The difference in the percentages of patients with an objective response and the 95% confidence intervals with strata weighting according to sample size were reported, and a separate analysis in which missing data were accounted for through multiple imputation was also conducted (see the Supplementary Methods section). Confidence intervals were not adjusted for multiplicity, so definitive treatment effects cannot be inferred.

The stratification factors that were used for randomization were applied to the analyses. The total familywise error rate (type I error) among the two primary efficacy end points and the secondary end point of objective response were strongly controlled at a two-sided alpha of 0.05. A prespecified graphical approach for multiplicity to control for type 1 error was used to test progression-free survival first in the pMMR population, then among all patients, followed by overall survival (first in the pMMR population and then among all patients) and then objective response (first in the pMMR population and then among all patients) (Fig. S1 in the Supplementary Appendix). For health-related quality-of-life analyses, global health status scores were summarized according to treatment group over time. The safety analysis population included all the patients who underwent randomization and received at least one dose of trial treatment. Further details are included in the Supplementary Methods section and the statistical analysis plan (see the protocol).

RESULTS

PATIENTS AND TREATMENTS

Across 167 sites in 21 countries, 827 patients (697 in the pMMR population and 130 in the dMMR population) were randomly assigned to a treatment group between June 11, 2018, and February 3, 2020 (Fig. S2). Data cutoff occurred on October 26, 2020, for the final analysis of progression-free survival and the first interim analysis of overall survival. The median follow-up was 12.2 months in the lenvatinib–pembrolizumab group and 10.7 months in the chemotherapy group. At the data-cutoff date, treatment was

ongoing in 27.8% of the patients in the pMMR population and in 30.5% of all the patients who started treatment in the lenvatinib–pembrolizumab group and in 2.8% and 2.6%, respectively, of those who started chemotherapy. The primary reason for treatment discontinuation among all the patients in all the groups was disease progression.

The demographic and disease characteristics of the patients at baseline were balanced between the treatment groups, both overall and in the pMMR population (Tables 1, S1, and S2). These populations were also determined to be equivalent to real-world populations (Table S3). Among all the patients, 84.2% of the patients in the lenvatinib–pembrolizumab group and 84.4% of those in the chemotherapy group had confirmed pMMR status, and 35.0% and 38.2% of the patients, respectively, had previously received systemic treatment only as neoadjuvant or adjuvant therapy. Treatment with one previous platinum-based therapy was reported for 79.3% of the patients in the lenvatinib–pembrolizumab group and for 75.7% of those in the chemotherapy group; 20.2% and 24.3% of the patients, respectively, had received two platinum-based therapies previously; 8.8% and 10.6% had received palliative hormonal therapy previously; and 46.0% and 47.8% had received external-beam radiotherapy previously.

EFFICACY

In the pMMR population, progression-free survival as assessed on blinded independent central review according to RECIST, version 1.1, was significantly longer with lenvatinib plus pembrolizumab (median, 6.6 months; 95% CI, 5.6 to 7.4) than with chemotherapy (median, 3.8 months; 95% CI, 3.6 to 5.0) (hazard ratio for progression or death, 0.60; 95% CI, 0.50 to 0.72; $P < 0.001$) (Fig. 1A). Similar results were seen in the overall trial population; the median progression-free survival was 7.2 months (95% CI, 5.7 to 7.6) with lenvatinib plus pembrolizumab, as compared with 3.8 months (95% CI, 3.6 to 4.2) with chemotherapy (hazard ratio, 0.56; 95% CI, 0.47 to 0.66; $P < 0.001$) (Fig. 1B).

Overall survival in the pMMR population was significantly longer with lenvatinib plus pembrolizumab (median, 17.4 months; 95% CI, 14.2 to 19.9) than with chemotherapy (median, 12.0 months; 95% CI, 10.8 to 13.3) (hazard ratio for

Table 1. Demographic and Disease Characteristics of All the Trial Patients at Baseline.*

Characteristic	Lenvatinib plus Pembrolizumab (N = 411)	Chemotherapy (N = 416)
Age		
Median (range) — yr	64 (30–82)	65 (35–86)
<65 yr — no. (%)	206 (50.1)	204 (49.0)
Race — no. (%)†		
White	261 (63.5)	246 (59.1)
Black	17 (4.1)	14 (3.4)
Asian	85 (20.7)	92 (22.1)
Geographic region — no. (%)‡		
Region 1	234 (56.9)	240 (57.7)
Region 2	177 (43.1)	176 (42.3)
MMR status — no. (%)		
pMMR	346 (84.2)	351 (84.4)
dMMR	65 (15.8)	65 (15.6)
ECOG performance-status score — no. (%)§		
0	246 (59.9)	241 (57.9)
1	164 (39.9)	175 (42.1)
History of pelvic irradiation — no. (%)	174 (42.3)	186 (44.7)
Histologic features at initial diagnosis — no. (%)¶		
Endometrioid carcinoma	243 (59.1)	254 (61.1)
High grade	94 (22.9)	90 (21.6)
Low grade	59 (14.4)	54 (13.0)
Not specified	90 (21.9)	110 (26.4)
Serous carcinoma	103 (25.1)	115 (27.6)
Clear-cell carcinoma	30 (7.3)	17 (4.1)
Mixed features	22 (5.4)	16 (3.8)

* Percentages may not total 100 because of rounding. The term dMMR denotes mismatch repair–deficient, MMR mismatch repair, and pMMR mismatch repair–proficient.

† Race was reported by the patient. Data on race were missing for 36 patients (8.8%) in the lenvatinib–pembrolizumab group and for 44 (10.6%) in the chemotherapy group. Other races or ethnic groups (reported by 12 patients [2.9%] in the lenvatinib–pembrolizumab group and by 20 [4.8%] in the chemotherapy group) included American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and multiple.

‡ Region 1 was defined as Australia, Canada, Europe, Israel, New Zealand, and the United States, and region 2 as the rest of the world.

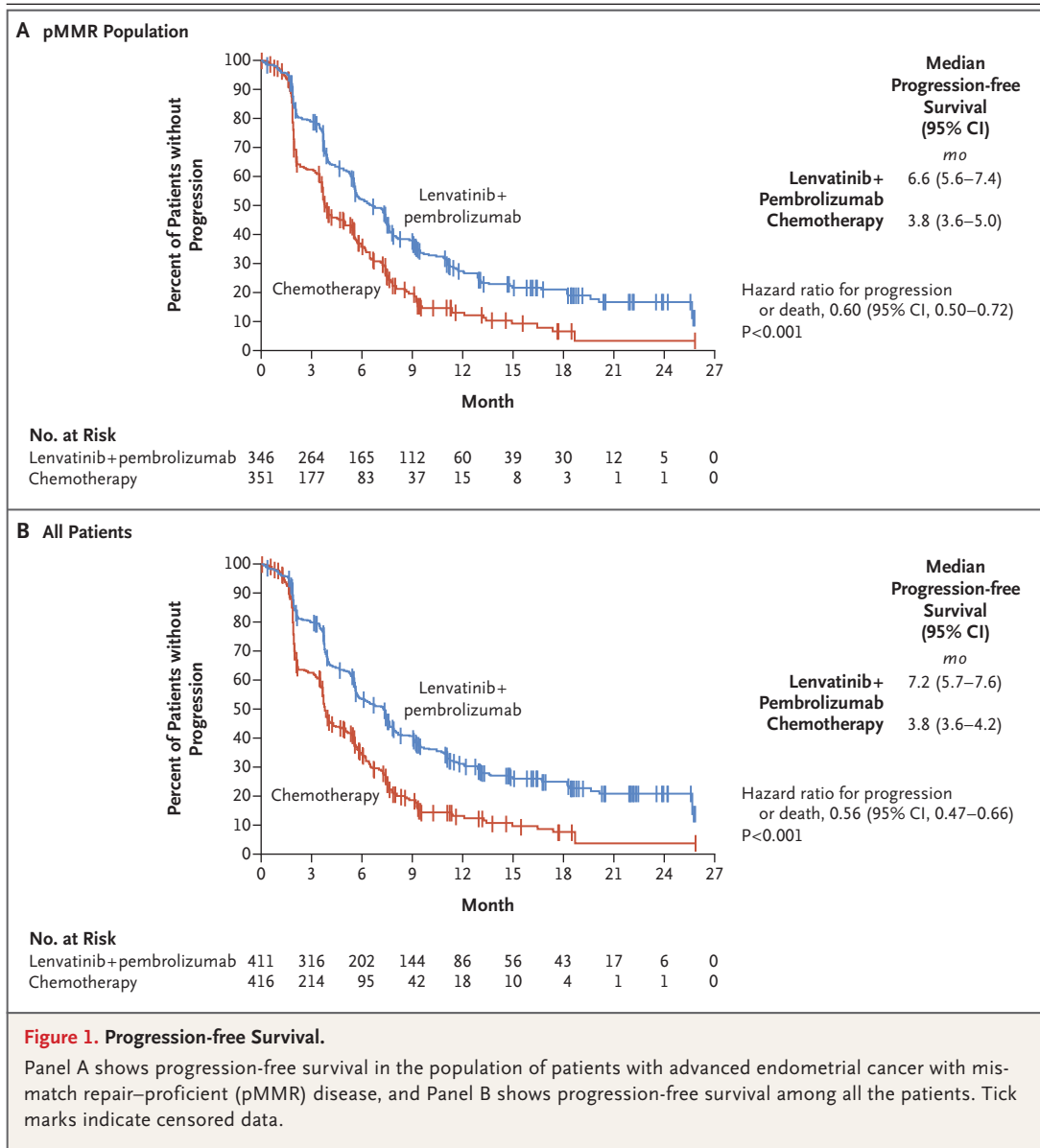
§ Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a 5-point scale, with higher scores indicating greater disability. One patient in the lenvatinib–pembrolizumab group had an ECOG performance-status score of 3 (was enrolled in error).

¶ Information regarding histologic features at diagnosis for categories that included less than 5% of the patients is provided in Table S2.

|| The “not specified” category included endometrioid carcinoma (grade not specified) and endometrioid carcinoma with squamous differentiation.

death, 0.68; 95% CI, 0.56 to 0.84; P<0.001) (Fig. 2A). Similar results were seen in the overall trial population; the median overall survival was 18.3 months (95% CI, 15.2 to 20.5) with lenvatinib plus pembrolizumab, as compared with 11.4 months (95% CI, 10.5 to 12.9) with chemo-

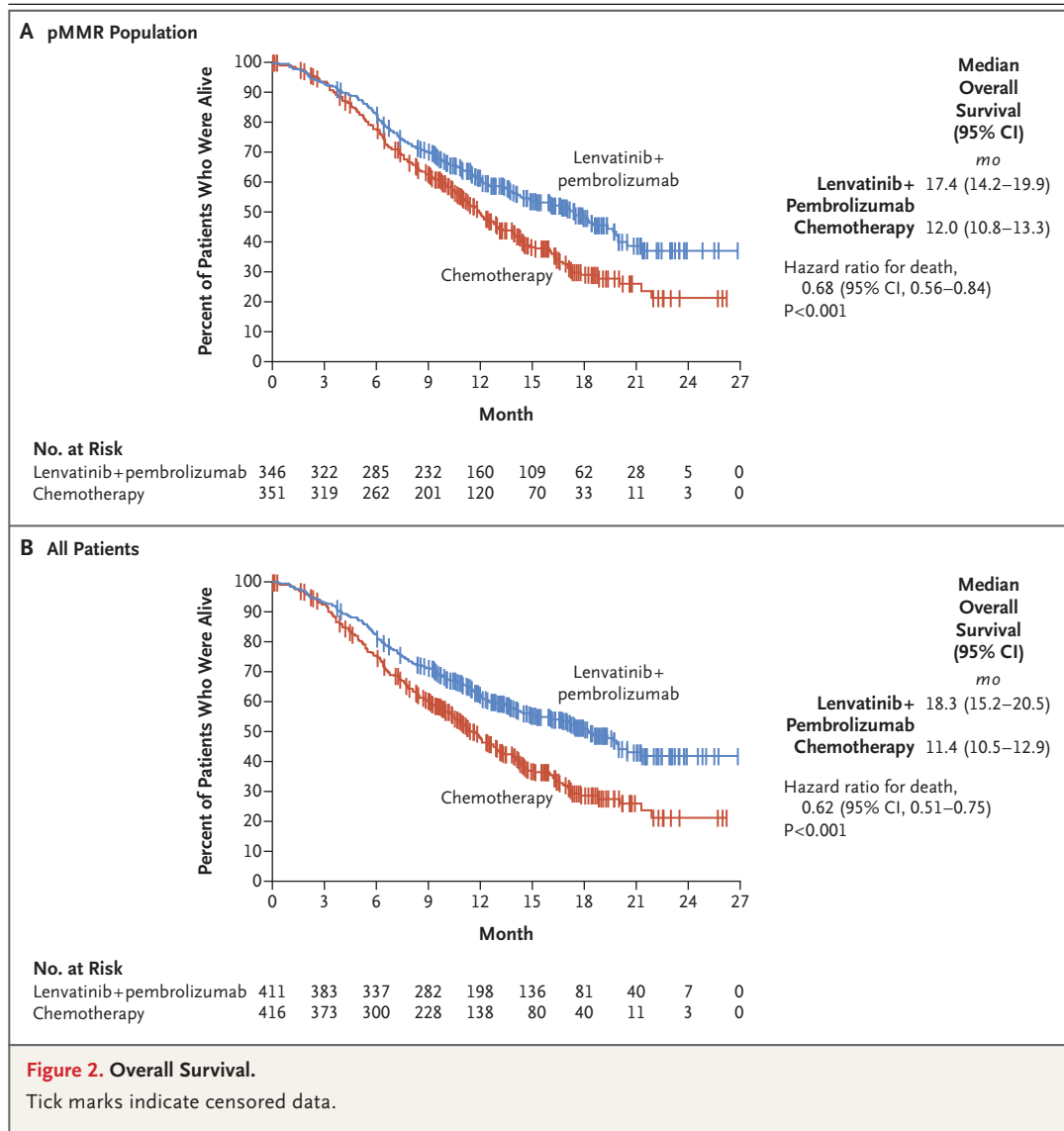
therapy (hazard ratio, 0.62; 95% CI, 0.51 to 0.75; P<0.001) (Fig. 2B). The proportional-hazards assumptions of progression-free survival and overall survival among all the patients were met, thus the hazards were deemed to be proportional (Fig. S3).



The results of the analyses of progression-free survival and overall survival favored the lenvatinib plus pembrolizumab group over the chemotherapy group across all the evaluated subgroups, including subgroups defined according to age, histologic features, and previous lines of therapy. Results were similar both in the pMMR population and among all the patients (Figs. S4 and S5).

In the pMMR population, the percentage of patients with a confirmed objective response as assessed on blinded independent central review according to RECIST, version 1.1, was higher with

lenvatinib plus pembrolizumab (30.3%) than with chemotherapy (15.1%); in the overall trial population, the percentages were 31.9% and 14.7%, respectively (Table 2). The results of the prespecified and multiple imputation analyses of objective response are reported in Table S4. In the pMMR population, 5.2% of the patients in the lenvatinib–pembrolizumab group and 2.6% of those in the chemotherapy group had a complete response; the corresponding percentages in the overall trial population were 6.6% and 2.6%. More patients (approximately twice as many) in the chemotherapy group than in the



lenvatinib–pembrolizumab group had a best response of progressive disease. Among patients with a response, the median duration of response in the pMMR population was 9.2 months (range, 1.6 to 23.7) with lenvatinib plus pembrolizumab and 5.7 months (range, 0.0 to 24.2) with chemotherapy; among patients with a response, the median duration of response in the overall trial population was 14.4 months (range, 1.6 to 23.7) and 5.7 months (95% CI, 0.0 to 24.2), respectively (Table 2 and Fig. S6).

Overall, more patients in the lenvatinib–pembrolizumab group than in the chemotherapy group had tumor shrinkage (Fig. S7). Although the trial was not designed or powered to com-

pare lenvatinib plus pembrolizumab with chemotherapy in the dMMR population, clinically meaningful improvement was observed across efficacy end points (Table 2 and Figs. S4, S5, S6, S8, and S9).

EXPOSURE AND SAFETY

In the safety analysis population, the median duration of treatment was 231 days (range, 1 to 817) with lenvatinib plus pembrolizumab and 104.5 days (range, 1 to 785) with chemotherapy (Table S5). Among patients receiving lenvatinib plus pembrolizumab, the median dose intensity of lenvatinib was 13.8 mg per day, and the median number of cycles of pembrolizumab was

Table 2. Confirmed Tumor Responses.*

End Point	pMMR Population		All Patients		dMMR Population	
	Lenvatinib plus Pembrolizumab (N=346)	Chemotherapy (N=351)	Lenvatinib plus Pembrolizumab (N=411)	Chemotherapy (N=416)	Lenvatinib plus Pembrolizumab (N=65)	Chemotherapy (N=65)
Objective response						
No. of patients	105	53	131	61	26	8
Percent (95% CI)	30.3 (25.5 to 35.5)	15.1 (11.5 to 19.3)	31.9 (27.4 to 36.6)	14.7 (11.4 to 18.4)	40 (28 to 53)	12 (5 to 23)
Best overall response						
Complete response						
No. of patients	18	9	27	11	9	2
Percent (95% CI)	5.2 (3.1 to 8.1)	2.6 (1.2 to 4.8)	6.6 (4.4 to 9.4)	2.6 (1.3 to 4.7)	14 (7 to 25)	3 (<1 to 11)
Partial response						
No. of patients	87	44	104	50	17	6
Percent (95% CI)	25.1 (20.7 to 30.1)	12.5 (9.3 to 16.5)	25.3 (21.2 to 29.8)	12.0 (9.1 to 15.5)	26 (16 to 39)	9 (3 to 19)
Stable disease						
No. of patients	168	139	193	167	25	28
Percent (95% CI)	48.6 (43.2 to 54.0)	39.6 (34.4 to 44.9)	47.0 (42.0 to 51.9)	40.1 (35.4 to 45.0)	38 (27 to 51)	43 (31 to 56)
Progressive disease						
No. of patients	54	108	61	123	7	15
Percent (95% CI)	15.6 (11.9 to 19.9)	30.8 (26.0 to 35.9)	14.8 (11.5 to 18.7)	29.6 (25.2 to 34.2)	11 (4 to 21)	23 (14 to 35)
Could not be evaluated†						
No. of patients	2	7	5	8	3	1
Percent (95% CI)	0.6 (0.1 to 2.1)	2.0 (0.8 to 4.1)	1.2 (0.4 to 2.8)	1.9 (0.8 to 3.8)	5 (1 to 13)	2 (0 to 8)
Not assessed‡						
No. of patients	17	44	21	57	4	13
Percent (95% CI)	4.9 (2.9 to 7.8)	12.5 (9.3 to 16.5)	5.1 (3.2 to 7.7)	13.7 (10.5 to 17.4)	6 (2 to 15)	20 (11 to 32)
Median duration of response (range) — mo§	9.2 (1.6 to 23.7)	5.7 (0.0 to 24.2)	14.4 (1.6 to 23.7)	5.7 (0.0 to 24.2)	NR (2.1 to 20.4)	4.1 (1.9 to 15.6)
Median time to response (range) — mo¶	2.1 (1.5 to 9.4)	3.5 (1.0 to 7.4)	2.1 (1.5 to 16.3)	2.1 (1.0 to 7.4)	2.9 (1.7 to 16.3)	1.9 (1.8 to 3.7)
Disease control¶¶						
No. of patients	248	163	296	194	48	31
Percent (95% CI)	71.7 (66.6 to 76.4)	46.4 (41.1 to 51.8)	72 (67.4 to 76.3)	46.6 (41.8 to 51.6)	74 (61 to 84)	48 (35 to 60)

* NR denotes not reached.

† A postbaseline assessment was available for these patients, but they could not be evaluated for response by the independent imaging vendor (e.g., owing to poor radiographic technique, poorly defined tumor margins, lesions that had been identified at screening not being imaged at a subsequent time point, or the lesion being obstructed by another body part and thus being unable to be measured or evaluated).

‡ No postbaseline assessment was available for response evaluation.

§ Duration of response was assessed only in patients with a complete or partial response.

¶ Disease control was defined as a best overall response of complete response, partial response, or stable disease at 7 weeks or more after randomization.

10. Among patients receiving chemotherapy, the median number of cycles was 5 for doxorubicin and 6 for paclitaxel. More patients in the lenvatinib-pembrolizumab group than in the chemotherapy group had durations of exposure of at least 6 months, at least 12 months, and at least 18 months (Table S6). The median time to the first dose reduction of lenvatinib was 1.9 months (range, 0.1 to 22.8); 45.6% of the patients in the lenvatinib-pembrolizumab group had two or more dose reductions of lenvatinib (Table S7).

Almost all the patients in the two treatment groups (>99%) had adverse events during treatment, with the most common being hypertension (in 64.0% of the patients) with lenvatinib plus pembrolizumab and anemia (in 48.7%) with chemotherapy (Table 3). Grade 3 or higher adverse events occurred in 88.9% of the patients receiving lenvatinib plus pembrolizumab and in 72.7% of those receiving chemotherapy. The most common serious adverse events were hypertension (in 4.2% of the patients) with lenvatinib plus pembrolizumab and febrile neutropenia (in 4.1%) with chemotherapy. Grade 5 adverse events (regardless of the investigator's assessment of relation to treatment) occurred in 5.7% of the patients receiving lenvatinib plus pembrolizumab and in 4.9% of those receiving chemotherapy.

The most frequent adverse events leading to dose reduction, treatment interruption, and trial-drug discontinuation are listed in Tables S8, S9, and S10, respectively. Among patients receiving lenvatinib plus pembrolizumab, adverse events of any grade led to dose reduction of lenvatinib in 66.5%, to interruption (of lenvatinib, pembrolizumab, or both) in 69.2%, and to trial-drug discontinuation in 33.0% (discontinuation of lenvatinib in 30.8%, of pembrolizumab in 18.7%, and of both in 14.0%). Among patients receiving chemotherapy, adverse events of any grade led to dose reduction in 12.9%, to interruption in 27.1%, and to trial-drug discontinuation in 8.0%. Details are provided in Table S11.

Adverse events related to trial therapy are elucidated in Table S12. Adverse events of interest with regard to pembrolizumab occurred in 67.2% of the patients; hypothyroidism was the most common, with an incidence of 57.6% (grade 1 in 17.2% and grade 2 in 38.9%) among patients who received lenvatinib plus pembrolizumab (Table S13). Clinically significant adverse

events with lenvatinib therapy are listed in Table S14, and serious adverse events that occurred in at least 1% of all the treated patients are listed in Table S15.

HEALTH-RELATED QUALITY OF LIFE

The QLQ-C30 was completed for more than 95% of the patients in the two treatment groups at baseline; scores at 12 weeks after randomization were available for 80% of the patients in the lenvatinib-pembrolizumab group and for 62% of those in the chemotherapy group. No substantial between-group differences were observed in the QLQ-C30 global health status quality-of-life scores over time (Fig. S10).

SUBSEQUENT THERAPY

In the intention-to-treat population, 28.0% of the patients in the lenvatinib-pembrolizumab group and 48.1% of those in the chemotherapy group received subsequent systemic anticancer medications. In the chemotherapy group, 9.1% of the patients in the pMMR population received lenvatinib plus pembrolizumab as subsequent therapy, and 16.9% of the patients in the dMMR population received PD-1 pathway-targeting monotherapy or combination regimens as subsequent therapies.

DISCUSSION

In this phase 3 trial, we compared lenvatinib plus pembrolizumab with physician's choice of chemotherapy in patients with advanced endometrial cancer whose disease had progressed or recurred after the receipt of at least one previous platinum-based chemotherapy regimen. With respect to the two primary efficacy end points, both progression-free survival and overall survival were significant longer with lenvatinib plus pembrolizumab than with chemotherapy, both in the pMMR population and among all the patients; these results address a need for effective therapy in these patient populations. The efficacy curves separated early during the course of trial therapy and remained consistently separated throughout the evaluation period. These benefits in progression-free survival and overall survival were seen across all evaluated subgroups, including subgroups defined according to less-common yet aggressive histologic features, history of pelvic irradiation, and previous lines of therapy.

Table 3. Adverse Events of Any Cause with an Incidence of 25% or More among All the Patients in Either Treatment Group, According to Preferred Term.

Event	Lenvatinib plus Pembrolizumab (N = 406)		Chemotherapy (N = 388)	
	Any Grade	Grade $\geq 3^*$	Any Grade	Grade $\geq 3^*$
Any adverse event	405 (99.8)	361 (88.9)	386 (99.5)	282 (72.7)
Hypertension [†]	260 (64.0)	154 (37.9)	20 (5.2)	9 (2.3)
Hypothyroidism ^{†‡}	233 (57.4)	5 (1.2)	3 (0.8)	0
Diarrhea	220 (54.2)	31 (7.6)	78 (20.1)	8 (2.1)
Nausea	201 (49.5)	14 (3.4)	179 (46.1)	5 (1.3)
Decreased appetite	182 (44.8)	32 (7.9)	82 (21.1)	2 (0.5)
Vomiting	149 (36.7)	11 (2.7)	81 (20.9)	9 (2.3)
Weight decrease	138 (34.0)	42 (10.3)	22 (5.7)	1 (0.3)
Fatigue	134 (33.0)	21 (5.2)	107 (27.6)	12 (3.1)
Arthralgia	124 (30.5)	7 (1.7)	31 (8.0)	0
Proteinuria [†]	117 (28.8)	22 (5.4)	11 (2.8)	1 (0.3)
Anemia	106 (26.1)	25 (6.2)	189 (48.7)	57 (14.7)
Constipation	105 (25.9)	3 (0.7)	96 (24.7)	2 (0.5)
Urinary tract infection	104 (25.6)	16 (3.9)	39 (10.1)	4 (1.0)
Neutropenia	30 (7.4)	7 (1.7)	131 (33.8)	100 (25.8)
Alopecia	22 (5.4)	0	120 (30.9)	2 (0.5)

* Among the patients who received lenvatinib plus pembrolizumab, 5.7% died owing to grade 5 adverse events (gastrointestinal disorder in 1.2% of the patients, cardiac disorder in 0.5%, general disorder in 1.5%, infection in 0.7%, decreased appetite in 0.2%, and neoplasms, nervous system disorder, psychiatric disorder, renal disorder, reproductive disorder, or respiratory disorder in 0.2% each). Among the patients who received chemotherapy, 4.9% died owing to grade 5 adverse events (cardiac disorder in 1.0%, general disorder in 1.3%, infection in 1.5%, subdural hematoma in 0.3%, and respiratory disorder in 0.8%).

[†] This event was a clinically significant adverse event with lenvatinib therapy (Table S14).

[‡] This event was an adverse event of interest with pembrolizumab therapy (Table S13).

Patients in the lenvatinib–pembrolizumab group had improved outcomes, including prolonged overall survival, as compared with those in the chemotherapy group, despite 9.1% of the patients in the pMMR population who had been assigned to the chemotherapy group receiving lenvatinib plus pembrolizumab as subsequent anticancer treatment and 16.9% of those in the dMMR population who had been assigned to the chemotherapy group receiving PD-1 pathway–targeting checkpoint monotherapy or combination therapies as subsequent treatments. The percentages of patients with an objective response associated with lenvatinib plus pembrolizumab treatment were consistent with previous findings from the phase 2 Study 111–KEYNOTE-146 trial²⁵ and were higher than the percentages observed in the chemotherapy group. Efficacy results with chemotherapy were consistent with

findings from phase 3 trials in the context of second-line or later treatment.^{9,10}

The most frequent adverse events (incidence of $\geq 30\%$ in the respective treatment groups) were hypertension, hypothyroidism, diarrhea, nausea, decreased appetite, vomiting, decreased body weight, fatigue, and arthralgia among patients receiving lenvatinib plus pembrolizumab and anemia, nausea, neutropenia, and alopecia among those receiving chemotherapy. The safety data for the combination therapy in our trial were generally consistent with the results observed in the Study 111–KEYNOTE-146 trial and the known adverse-event profiles of each agent.^{19,24,25,27-31} The incidence of hypothyroidism (an adverse event that has been associated with both lenvatinib and pembrolizumab treatment),^{17,32} although higher than with chemotherapy in this trial or individual monotherapies in earlier trials,^{29,30}

was detected by means of surveillance and corrected easily with oral medication, and most events were of grade 1 or 2 severity. The strategy of administering lenvatinib therapy by starting at the established dose and reducing as necessary has previously been successful.²⁵ Although a small-scale retrospective study³³ has suggested that a starting dose of 14 mg per day does not compromise efficacy, that study involved a small number of patients (70 enrolled, of which only 16 were treated at a dose of 20 mg per day). Prospective studies (with larger populations) have involved patients with other tumor types and have indicated that lower starting doses were not noninferior to the approved starting dose of lenvatinib for the treatment of renal-cell carcinoma and differentiated thyroid cancer.^{34,35} Moreover, safety was not noticeably improved at lower starting doses.^{34,35} In our trial, adverse events of any cause led to dose reductions in 66.5% of the patients who received lenvatinib plus pembrolizumab.

A limitation of this trial is the relatively short duration of follow-up, which may mean that responses are evolving. Although the protocol-specified criteria were met for the efficacy analyses, safety and efficacy monitoring is ongoing.

This trial showed that treatment with lenvatinib plus pembrolizumab led to significantly longer progression-free survival and overall survival than chemotherapy of the treating physician's choice, both in the pMMR population and in the overall trial population of patients with advanced endometrial cancer who had disease progression after the receipt of previous systemic platinum-based therapy.

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APPENDIX

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