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Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer

Vicky Makker, MD¹; Matthew H. Taylor, MD²; Carol Aghajanian, MD¹; Ana Oaknin, MD, PhD³; James Mier, MD⁴; Allen L. Cohn, MD⁵; Margarita Romeo, MD, PhD⁶; Raquel Bratos, MD⁷; Marcia S. Brose, MD, PhD⁸; Christopher DiSimone, MD⁹; Mark Messing, MD¹⁰; Daniel E. Stepan, MD¹¹; Corina E. Dutcus, MD¹²; Jane Wu, PhD¹²; Emmett V. Schmidt, MD, PhD¹³; Robert Orłowski, MD¹³; Pallavi Sachdev, PhD¹²; Robert Shumaker, PhD¹¹; and Antonio Casado Herraes, MD, PhD¹⁴

PURPOSE Patients with advanced endometrial carcinoma have limited treatment options. We report final primary efficacy analysis results for a patient cohort with advanced endometrial carcinoma receiving lenvatinib plus pembrolizumab in an ongoing phase Ib/II study of selected solid tumors.

METHODS Patients took lenvatinib 20 mg once daily orally plus pembrolizumab 200 mg intravenously once every 3 weeks, in 3-week cycles. The primary end point was objective response rate (ORR) at 24 weeks (ORR_{Wk24}); secondary efficacy end points included duration of response (DOR), progression-free survival (PFS), and overall survival (OS). Tumor assessments were evaluated by investigators per immune-related RECIST.

RESULTS At data cutoff, 108 patients with previously treated endometrial carcinoma were enrolled, with a median follow-up of 18.7 months. The ORR_{Wk24} was 38.0% (95% CI, 28.8% to 47.8%). Among subgroups, the ORR_{Wk24} (95% CI) was 63.6% (30.8% to 89.1%) in patients with microsatellite instability (MSI)-high tumors (n = 11) and 36.2% (26.5% to 46.7%) in patients with microsatellite-stable tumors (n = 94). For previously treated patients, regardless of tumor MSI status, the median DOR was 21.2 months (95% CI, 7.6 months to not estimable), median PFS was 7.4 months (95% CI, 5.3 to 8.7 months), and median OS was 16.7 months (15.0 months to not estimable). Grade 3 or 4 treatment-related adverse events occurred in 83/124 (66.9%) patients.

CONCLUSION Lenvatinib plus pembrolizumab showed promising antitumor activity in patients with advanced endometrial carcinoma who have experienced disease progression after prior systemic therapy, regardless of tumor MSI status. The combination therapy had a manageable toxicity profile.

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INTRODUCTION

The incidence and disease-related mortality of endometrial cancer, the most common gynecologic cancer in the United States, continues to increase.¹⁻⁴

Although early-stage endometrial carcinoma is associated with a favorable 5-year relative survival rate (96%),⁵ the rate is 18% in patients with distant metastases.⁵

Paclitaxel plus carboplatin is standard first-line treatment of advanced, recurrent, and metastatic endometrial carcinoma.^{6,7} Until recently, only 2 other therapies were specifically approved in the metastatic setting.⁸ Megestrol acetate is approved for the palliative treatment of advanced endometrial carcinoma, regardless of platinum use.⁹ Pembrolizumab, a monoclonal antibody targeting programmed death receptor-1 (PD-1), is broadly (ie, tissue agnostic) approved for microsatellite instability-high (MSI-H)/mismatch-repair-deficient (dMMR) solid tumors that have

progressed after prior therapy and have no satisfactory alternative treatment options.¹⁰ Accordingly, pembrolizumab is used for metastatic MSI-H endometrial carcinoma after front-line chemotherapy failure.

MSI-H tumors with high mutational burdens are more susceptible to checkpoint inhibitors,¹¹ and the mutational burden in MSI-H endometrial cancers is particularly high.¹² Pembrolizumab has demonstrated efficacy in patients with MSI-H endometrial cancer. In a phase II study of pembrolizumab monotherapy in patients with previously treated advanced MSI-H/dMMR noncolorectal cancer, results from the endometrial cohort (n = 49) demonstrated an objective response rate (ORR) of 57.1% (95% CI, 42.2% to 71.2%), with a median progression-free survival (PFS) of 25.7 months (95% CI, 4.9 months to not reached).^{13,14} However, MSI-H endometrial cancers comprise only 16% of recurrent disease cases.¹⁵ In a phase Ib study of pembrolizumab for advanced programmed death ligand-1 (PD-L1)-positive

ASSOCIATED CONTENT

Protocol

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TABLE 1. Demographics and Baseline Characteristics

Parameter	Previously Treated EC ^a			All EC (N = 124)
	MSS/pMMR (n = 94)	MSI-H/dMMR (n = 11)	Total ^b (n = 108)	
Age, years, mean (SD)	65.4 (7.42)	62.4 (9.45)	65.1 (7.60)	65.3 (7.83)
Race				
White	81 (86.2)	9 (81.8)	93 (86.1)	108 (87.1)
Black or African American	6 (6.4)	0	6 (5.6)	7 (5.6)
Asian	4 (4.3)	1 (9.1)	5 (4.6)	5 (4.0)
American Indian or Alaskan Native	1 (1.1)	0	1 (0.9)	1 (0.8)
Native Hawaiian or other Pacific Islander	0	1 (9.1)	1 (0.9)	1 (0.8)
Other	2 (2.1)	0	2 (1.9)	2 (1.6)
ECOG PS				
0	49 (52.1)	1 (9.1)	53 (49.1)	62 (50.0)
1	45 (47.9)	10 (90.9)	55 (50.9)	62 (50.0)
Histologic subtype				
Endometrioid adenocarcinoma	46 (48.9)	8 (72.7)	55 (50.9)	67 (54.0)
FIGO grade 1	10 (10.6)	2 (18.2)	12 (11.1)	15 (12.1)
FIGO grade 2	15 (16.0)	4 (36.4)	19 (17.6)	22 (17.7)
FIGO grade 3	21 (22.3)	2 (18.2)	24 (22.2)	30 (24.2)
Serous adenocarcinoma	33 (35.1)	0	35 (32.4)	39 (31.5)
Clear-cell adenocarcinoma	5 (5.3)	1 (9.1)	6 (5.6)	6 (4.8)
Dedifferentiated/undifferentiated carcinoma	0	1 (9.1)	1 (0.9)	1 (0.8)
Adenocarcinoma, not otherwise specified	1 (1.1)	0	1 (0.9)	1 (0.8)
Other ^c	9 (9.6)	1 (9.1)	10 (9.3)	10 (8.1)
PD-L1 status ^d				
Positive	46 (48.9)	7 (63.6)	53 (49.1)	60 (48.4)
Negative	39 (41.5)	4 (36.4)	43 (39.8)	52 (41.9)
Not available	9 (9.6)	0	12 (11.1)	12 (9.7)
Prior treatment regimens for endometrial carcinoma ^e				
0	0	0	0	9 (7.3)
1	48 (51.1)	7 (63.6)	57 (52.8)	60 (48.4)
2	36 (38.3)	3 (27.3)	40 (37.0)	43 (34.7)
≥ 3	10 (10.6)	1 (9.1)	11 (10.2)	12 (9.7)

(continued on following page)

endometrial cancer (in patients whose disease progressed after standard therapy or for whom standard therapy was not appropriate), 18 of 19 patients with evaluable tumor samples had microsatellite-stable (MSS) cancer.¹⁶ For all patients in the efficacy analysis (n = 23), the ORR was 13% (95% CI, 2.8% to 33.6%), with median PFS of 1.8 months (95% CI, 1.6 to 2.7 months), suggesting that pembrolizumab monotherapy may be less effective in patients with MSS tumors.

Lenvatinib is an oral multikinase inhibitor that targets vascular endothelial growth factor receptors 1-3, fibroblast growth factor receptors 1-4, platelet-derived growth factor receptor- α , RET, and KIT.¹⁷⁻¹⁹ In a phase II study of lenvatinib monotherapy for advanced, previously treated endometrial cancer, the ORR was 14.3% (as assessed by independent imaging review [IIR] per RECIST version 1.1²⁰), and the median PFS was 5.4 months.²¹

The combination of immune checkpoint inhibitors with lenvatinib has been evaluated in preclinical mouse xenograft studies.²²⁻²⁴ In these studies, lenvatinib plus PD-1/PD-L1 signal inhibitors had more potent antitumor activity than either agent alone.²²⁻²⁴ KEYNOTE-146/Study 111 (a phase Ib/II study) evaluated this combination in patients with advanced tumors.²⁵ In an interim cohort analysis (activity data cutoff: December 15, 2017; median study follow-up: 13 months) of patients with advanced endometrial cancer who were selected regardless of PD-L1 status, histology, or tumor MSI status, lenvatinib plus pembrolizumab demonstrated promising efficacy: objective response at week 24, assessed using immune-related RECIST (irRECIST), was achieved by 39.6% of the 53 patients (investigator assessment; 45.3%, IIR).²⁶ Here we present the final primary efficacy analysis results of the cohort of patients from KEYNOTE-146/Study 111 with advanced endometrial cancer.

METHODS

Study Design and Patients

KEYNOTE-146/Study 111 is an ongoing multinational, open-label, single-arm study (ClinicalTrials.gov identifier: [NCT02501096](https://clinicaltrials.gov/ct2/show/study/NCT02501096)) of lenvatinib plus pembrolizumab in patients with selected solid tumors (ie, non-small-cell lung cancer, renal cell carcinoma, endometrial carcinoma, urothelial carcinoma, squamous cell carcinoma of the head and neck, or melanoma). Eligibility criteria for the endometrial cohort have been published,²⁶ and a brief overview is provided in the Data Supplement.

This study was conducted in accordance with the guidelines of Good Clinical Practice (defined by the International Council on Harmonization) and the principles of the Declaration of Helsinki; the protocol was approved by the institutional review board or ethics committee at each participating center, and all patients provided written informed consent.

TABLE 1. Demographics and Baseline Characteristics (continued)

Parameter	Previously Treated EC ^a			
	MSS/pMMR (n = 94)	MSI-H/dMMR (n = 11)	Total ^b (n = 108)	All EC (N = 124)
No. of patients previously treated with bevacizumab	5 (5.3)	1 (9.1)	6 (5.6)	7 (5.6)
Prior treatments for endometrial carcinoma ^f				
Platinum + taxane combination (with or without other anticancer medication)	92 (97.9)	11 (100.0)	106 (98.1)	113 (91.1)
Other anticancer combinations	9 (9.6)	1 (9.1)	11 (10.2)	12 (9.7)
Monotherapy	33 (35.1)	3 (27.3)	36 (33.3)	37 (29.8)
Prior history of/current hypertension	60 (63.8)	9 (81.8)	71 (65.7)	79 (63.7)

NOTE. Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CPS, combined positive score; dMMR, mismatch-repair deficient; EC, endometrial carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FIGO, International Federation of Gynecology and Obstetrics; MSI-H, microsatellite instability high; MSI/MMR, microsatellite instability/mismatch repair; PD-L1, programmed death-ligand 1; pMMR, mismatch-repair proficient; SD, standard deviation.

^aEnrolled before July 1, 2018.

^bThree patients had an unknown MSI/MMR tumor status.

^cPredominantly mixed histology.

^dPD-L1 status is positive if CPS is ≥ 1 and negative if CPS is < 1 .

^eThe majority of patients received therapies in the adjuvant or metastatic setting; 9 patients received therapy in the neoadjuvant setting; the setting for 2 patients was unknown.

^fPatients may be counted in multiple categories.

Procedures and Study End Points

On the basis of the phase Ib dose-finding results,²⁵ patients were administered lenvatinib 20 mg once daily orally and pembrolizumab 200 mg intravenously once every 3 weeks in 3-week cycles (maximum of 35 pembrolizumab treatments).

The primary end point in this study was ORR at week 24 (ORR_{WK24}). Responses were confirmed by a second assessment ≥ 4 weeks after initial response. Secondary end points included ORR, duration of response (DOR), PFS, overall survival (OS), disease control rate (DCR; defined as the proportion of patients with a best overall response of complete response [CR], partial response [PR], or stable disease), and clinical benefit rate (CBR; defined as the proportion of patients with CR, PR, or durable stable disease [defined as stable disease ≥ 23 weeks]). Tumor responses for primary and secondary end points were assessed by the investigator per irRECIST.²⁷

Prespecified exploratory end points included tumor responses per irRECIST²⁷ and RECIST version 1.1²⁰ by IIR

(assessed by BioTel Research, BioTelemetry), and antitumor activity according to PD-L1 status. Activity by tumor histology and MSI status were post hoc exploratory analyses. Adverse events (AEs) were assessed according to Common Terminology Criteria for Adverse Events version 4.03.

For all patients, tumor assessments (investigator assessment and IIR) were completed at baseline, every 6 weeks for the first 24 weeks, and every 9 weeks thereafter. PD-L1 status was determined using an investigational version of the PD-L1 immunochemistry 22C3pharmDx²⁸ and a provisional combined positive score (defined as the number of staining tumor and immune cells relative to total tumor cells) cutoff of 1. Central testing to determine MSI was conducted using the MSI Analysis System, and central testing for mismatch repair (MMR) status was conducted using the Ventana MMR Immunohistochemical Assay. Available data regarding known MSI/MMR status based on local testing per institutional guidelines was also collected.

Toxicity was managed by supportive medications, treatment interruption, dose reduction (lenvatinib only; re-escalation was not allowed), and/or treatment discontinuation in accordance with predefined dose-modification guidelines. Information regarding treatment discontinuation of either lenvatinib or pembrolizumab and patient assessments during the follow-up period of this study can be found in the Data Supplement.

Statistical Methods

The phase II portion was designed to expand to 20 patients with endometrial cancer on the basis of efficacy and safety results. A protocol amendment allowed further expansion to a total sample size of ~120 patients after predetermined criteria of 2 interim analyses were met. Details regarding sample size determination can be found in the Data Supplement.

Efficacy analyses focused on patients who previously received systemic treatment; the primary analysis was planned for patients from the full analysis set who completed 8 cycles of treatment and had week 24 tumor assessments or who had discontinued early because of progressive disease, unacceptable toxicity, withdrawn consent, or study termination by the sponsor at the time of data cutoff. According to an addendum to the statistical analyses (made before database lock), data cutoff was when ≥ 100 patients with histologically confirmed, previously treated endometrial carcinoma had sufficient follow-up to provide a median follow-up of ≥ 12 months, and ≥ 6 months of follow-up after initial objective response for all responders.

Additional efficacy analyses are reported for previously treated and treatment-naïve patients (Data Supplement), regardless of their follow-up time at data cutoff. These efficacy analyses were based on the intention-to-treat population (ie, all patients with endometrial cancer who entered the study treatment period). Safety analyses were

TABLE 2. Summary of Tumor Response as Assessed by Investigators per Immune-Related RECIST

Response Category	Previously Treated EC ^a			All EC (N = 124)
	MSS/pMMR (n = 94)	MSI-H/dMMR (n = 11)	Total (n = 108)	
Week 24				
Best overall response				
Complete response	2 (2.1)	1 (9.1)	3 (2.8)	3 (2.4)
Partial response	32 (34.0)	6 (54.5)	38 (35.2)	46 (37.1)
Stable disease	45 (47.9)	3 (27.3)	50 (46.3)	56 (45.2)
Progressive disease	10 (10.6)	1 (9.1)	12 (11.1)	13 (10.5)
Not evaluable	5 (5.3)	0	5 (4.6)	6 (4.8)
Objective response rate (complete response + partial response)	34 (36.2)	7 (63.6)	41 (38.0)	49 (39.5)
95% CI	26.5 to 46.7	30.8 to 89.1	28.8 to 47.8	30.9 to 48.7
At data cutoff				
Best overall response				
Complete response	7 (7.4)	1 (9.1)	8 (7.4)	8 (6.5)
Partial response	28 (29.8)	6 (54.5)	34 (31.5)	42 (33.9)
Stable disease	44 (46.8)	3 (27.3)	49 (45.4)	55 (44.4)
Progressive disease	10 (10.6)	1 (9.1)	12 (11.1)	13 (10.5)
Not evaluable	5 (5.3)	0	5 (4.6)	6 (4.8)
Objective response rate (complete response + partial response)	35 (37.2)	7 (63.6)	42 (38.9)	50 (40.3)
95% CI	27.5 to 47.8	30.8 to 89.1	29.7 to 48.7	31.6 to 49.5
Disease control rate	79 (84.0)	10 (90.9)	91 (84.3)	105 (84.7)
95% CI	75.0 to 90.8	58.7 to 99.8	76.0 to 90.6	77.1 to 90.5
Clinical benefit rate	55 (58.5)	8 (72.7)	63 (58.3)	73 (58.9)
95% CI	47.9 to 68.6	39.0 to 94.0	48.5 to 67.7	49.7 to 67.6
Duration of response, months				
Median (95% CI)	NE (7.4 to NE)	21.2 (7.3 to NE)	21.2 (7.6 to NE)	NE (8.5 to NE)
No. of patients with duration of response, probability, Kaplan-Meier estimate				
≥ 6 months	25	7	32	36
Probability (95% CI)	0.85 (0.67 to 0.93)	1.00 (NE to NE)	0.87 (0.72 to 0.95)	0.87 (0.73 to 0.94)
≥ 12 months	9	3	12	12
Probability (95% CI)	0.60 (0.39 to 0.75)	0.80 (0.20 to 0.97)	0.63 (0.45 to 0.77)	0.65 (0.47 to 0.78)
Time to response, months, mean (SD)	2.5 (1.53)	2.9 (1.84)	2.6 (1.57)	2.5 (1.51)
Maximum tumor shrinkage in sum of diameters of target lesions, %, n/m ^b				
> 0	75/89 (84.3)	8/10 (80.0)	86/102 (84.3)	101/117 (86.3)
≥ 50	25/89 (28.1)	6/10 (60.0)	31/102 (30.4)	36/117 (30.8)
≥ 75	11/89 (12.4)	2/10 (20.0)	13/102 (12.7)	16/117 (13.7)

NOTE. Data are presented as No. (%) unless otherwise indicated.

Abbreviations: dMMR, mismatch-repair deficient; EC, endometrial carcinoma; MSI-H, microsatellite instability-high; MSI/MMR, microsatellite instability/mismatch repair; MSS, microsatellite stable; NE, not estimable; pMMR, mismatch-repair proficient; SD, standard deviation.

^aEnrolled before July 1, 2018; 3 patients had an unknown MSI/MMR tumor status.

^bm is the number of patients with both baseline and post-baseline sum of diameters of target lesions and is used as the denominator for the respective percentages.

based on the safety set, defined as all patients (previously treated and treatment naïve) who received any amount of study drug, irrespective of their follow-up time at data cutoff. The most common treatment-related AEs were reported by preferred terms or “baskets” (ie, groups of related preferred terms). Treatment-emergent prespecified AEs, serious treatment-related AEs, and deaths were reported by preferred terms.

Statistical analyses were performed using SAS (SAS Institute) version 9.4. ORR_{WK24} and the exact 95% CIs were calculated with the Clopper-Pearson method, as were 95% CIs for ORR, DCR, and CBR. Patients who did not have an evaluable tumor assessment were included in the denominator for the calculation of ORR. Medians of PFS and OS (and their median follow-up times) and DOR were estimated with the Kaplan-Meier method, and 95% CIs were calculated with a generalized Brookmeyer and Crowley method. Probabilities of patients achieving a DOR ≥ 6 months or ≥ 12 months were calculated using the Kaplan-Meier product-limit method and the Greenwood formula.

RESULTS

Patients

When enrollment (starting September 10, 2015) reached 118 patients (July 1, 2018), end-of-enrollment notifications were sent to study sites. At the time of notification, 7 additional patients who had completed screening were allowed to enroll in the endometrial carcinoma cohort (Data Supplement). Of the 125 enrolled patients, 1 had a major protocol violation—her primary tumor was determined to be a uterine leiomyosarcoma.

Analysis of the primary end point focused on the 108 patients with endometrial carcinoma who enrolled before July 1, 2018 and had previously received systemic therapy; these patients met all previously described conditions for the primary analysis at time of data cutoff (January 10,

2019; Data Supplement). The median follow-up for these patients was 18.7 months (95% CI, 13.1 to 20.3 months), and 29 (26.9%) patients were receiving ongoing study treatment with at least 1 study drug at data cutoff. The most common histologic subtypes of disease were endometrioid adenocarcinoma (50.9%; International Federation of Gynecology and Obstetrics [FIGO] grade 1 or 2, 28.7%; FIGO grade 3, 22.2%) and serous carcinoma (32.4%; Table 1). Nearly half (49.1%) of the patients were PD-L1 positive. Ninety-four (87.0%) and 11 (10.2%) patients were MSS or MMR proficient (pMMR) and MSI-H or dMMR, respectively (Table 1).

Efficacy

The primary end point, ORR_{WK24} , was 38.0% (41/108 patients; 95% CI, 28.8% to 47.8%; Table 2). In the 102 patients with evaluable tumor assessments by investigators per irRECIST, the sum of diameters of target lesions decreased (any size) from baseline in 86 (84.3%) patients (Fig 1; Table 2); 31 (30.4%) had a maximum decrease of $\geq 50\%$ and 13 (12.7%) had a maximum decrease of $\geq 75\%$ (Table 2).

Regarding secondary end points, the ORR of patients previously treated for endometrial carcinoma was 38.9% (42/108, 95% CI, 29.7% to 48.7%; CR, 8/108, 7.4%, 95% CI, 3.3% to 14.1%; PR, 34/108, 31.5%, 95% CI, 22.9% to 41.1%) and the median DOR was 21.2 months (95% CI, 7.6 months to not estimable [NE]; Table 2; Fig 2A). Among responders, the Kaplan-Meier estimate of the probability of a DOR ≥ 6 months was 87% (95% CI, 72% to 95%), and the Kaplan-Meier estimate of the probability of a DOR ≥ 12 months was 63% (95% CI, 45% to 77%; Table 2). Median PFS was 7.4 months (95% CI, 5.3 to 8.7 months; median follow-up: 11.9 months; 95% CI, 9.9 to 18.4 months; Fig 2B) and median OS was 16.7 months (95% CI, 15.0 months to NE; Fig 2C).

Tumor responses were similar irrespective of investigator or IIR and tumor response criteria (Data Supplement). Of

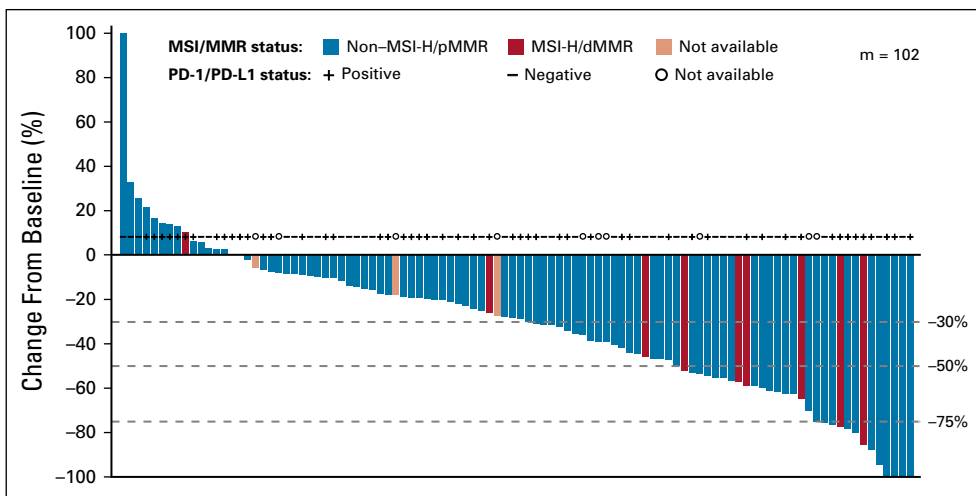


FIG 1. Percentage change in sum of diameters of target lesions from baseline to post-baseline nadir by microsatellite instability/mismatch-repair (MSI/MMR) status (by investigator assessment; using immune-related RECIST). dMMR, MMR deficient; m, the number of previously treated patients with both baseline and at least 1 postbaseline target lesion assessment; MSI-H, MSI-high; pMMR, MMR proficient; PD-1, programmed death receptor-1; PD-L1, programmed death-ligand 1.

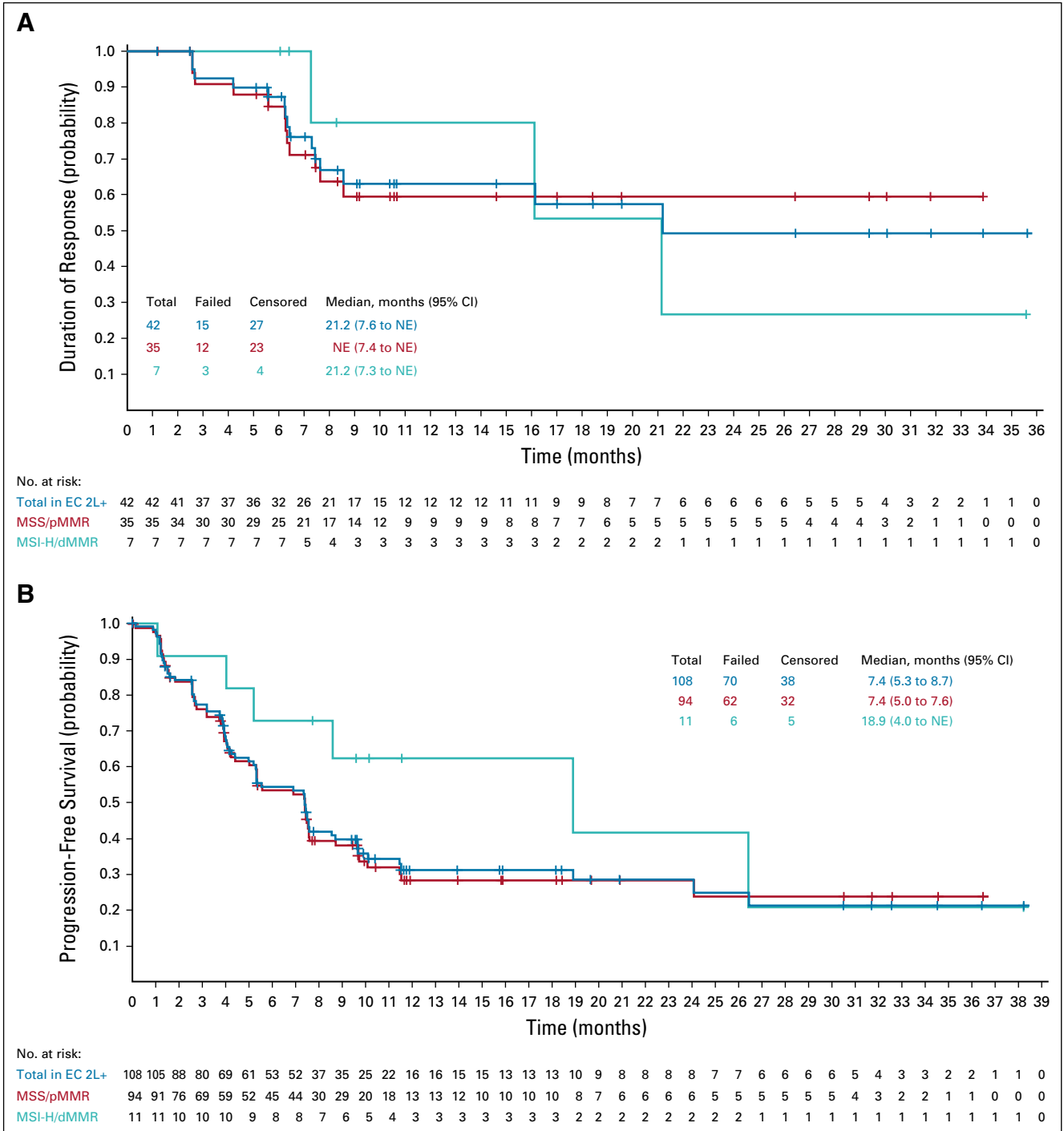


FIG 2. Kaplan-Meier plot of (A) duration of response, (B) progression-free survival, and (C) overall survival assessed by the investigator per immune-related RECIST (for A and B groups only; not appropriate for C) in patients with endometrial cancer previously treated with systemic therapies. dMMR, mismatch-repair deficient; EC 2L+, endometrial cancer second-line (or greater) treatment MSI-H, microsatellite instability high; MSS, microsatellite stable; NE, not estimable; pMMR, mismatch-repair proficient.

note, 35.8% (19/53; 95% CI, 23.1% to 50.2%) of patients with PD-L1–positive tumors and 39.5% (17/43; 95% CI, 25.0% to 55.6%) of patients with PD-L1–negative tumors had objective responses by investigator assessment per irRECIST (Data Supplement). For patients with MSS/pMMR

tumors, ORR—as assessed by investigators per irRECIST—was 37.2% (35/94; 95% CI, 27.5% to 47.8%). For patients with MSI-H/dMMR tumors, ORR was 63.6% (7/11; 95% CI, 30.8% to 89.1%; Table 2). Median DOR was NE (95% CI, 7.4 months to NE) for patients with MSS/pMMR tumors and

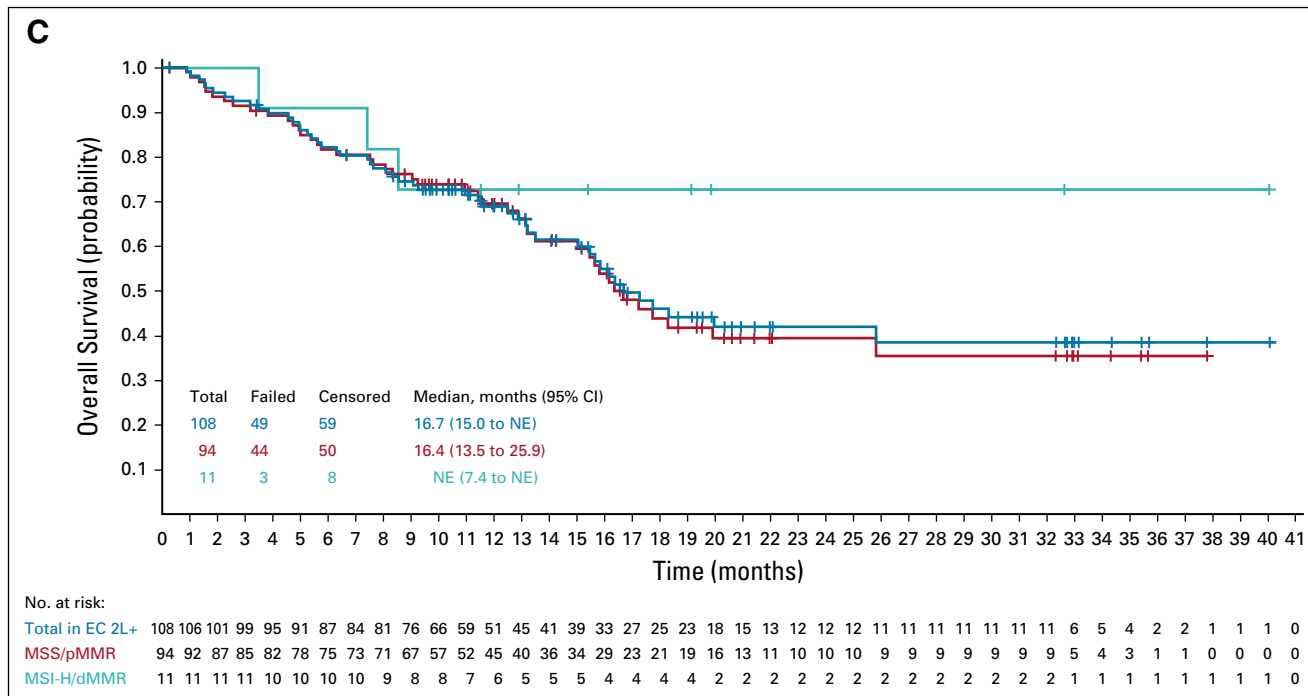


FIG 2. (Continued).

21.2 months (95% CI, 7.3 months to NE) for patients with MSI-H/dMMR tumors (Table 2; Fig 2A). Details regarding median PFS and OS by tumor MSI status are shown in Figures 2B and 2C, respectively. Additional details of responses by MSI and PD-L1 status are shown in the Data Supplement; the percentage changes in the sums of diameters of target lesions at post-baseline nadir by histologic subtype are shown in Figure 3 (by investigator assessment; using irRECIST) and the Data Supplement (by IIR; using RECIST version 1.1). Tumor responses by histologic subtypes are shown in the Data Supplement.

Safety

Mean duration of treatment with lenvatinib plus pembrolizumab was 8.5 months (8.2 months, lenvatinib and 7.3 months, pembrolizumab). Any-grade treatment-related AEs occurred in 120 (96.8%) patients. Grade 3 or 4 treatment-related AEs occurred in 83 (66.9%) patients (Table 3). Overall, 22 (17.7%) patients discontinued 1 or both study drugs because of treatment-related AEs (19 [15.3%] discontinued lenvatinib, 15 [12.1%] discontinued pembrolizumab, and 11 [8.9%] discontinued both study drugs). Treatment-related AEs led to dose interruptions of lenvatinib and/or pembrolizumab in 87 (70.2%) patients and dose reductions of lenvatinib in 78 (62.9%) patients. The mean dose intensity of lenvatinib was 14.4 mg/day (standard deviation [SD], 4.3), and the mean dose of lenvatinib received as a percentage of the planned dose was 71.9% (SD, 21.4). The mean duration of treatment with lenvatinib at each dose level is reported in the Data

Supplement; 11 (8.9%) patients remained on lenvatinib for ≥ 6 months after cycle 1 day 1 with no dose reductions.

The most common any-grade treatment-related AEs and the most common grade 3 or 4 treatment-related AEs are reported in Table 3 and the Data Supplement, respectively. Seventy-one patients (57.3%) experienced treatment-emergent, prespecified AEs associated with pembrolizumab. Hypothyroidism was the most frequent of these AEs, occurring in 59 (47.6%) patients.

Serious treatment-related AEs are reported in the Data Supplement. Fifty-one deaths occurred during this study: 16 while receiving study drug and 35 during follow-up—with a median time from last dose to death of 171 days (29/35 patients discontinued because of radiologic progression; cause of death during follow-up was not recorded). Of note, 4 deaths were considered caused by treatment-emergent AEs (1 each due to GI perforation, intestinal obstruction, general physical health deterioration, and metabolic encephalopathy) not deemed treatment related, and 2 deaths were judged to be treatment related (1 due to sepsis caused by an *Escherichia coli* infection and 1 due to intracranial hemorrhage).

DISCUSSION

Advanced endometrial carcinomas have a poor prognosis; the continued annual increase in incidence and disease-related mortality of endometrial cancer^{1,3,29} underscores a dire need to improve therapeutics for this malignancy.

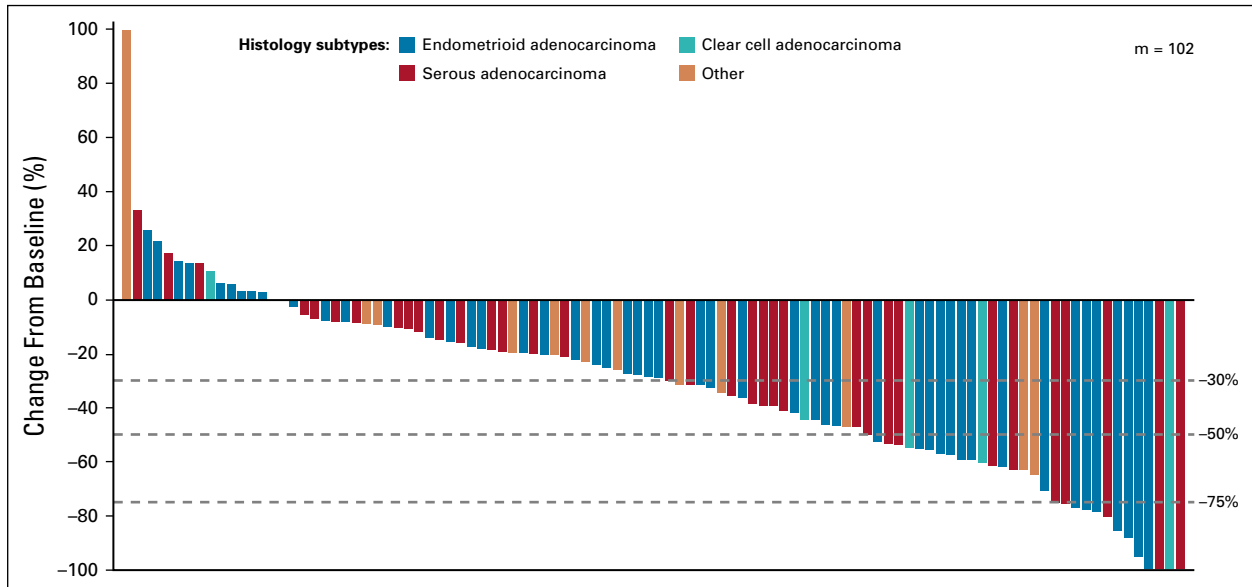


FIG 3. Percentage change in sum of diameters of target lesions from baseline to post-baseline nadir by histologic subtype (by investigator assessment; using immune-related RECIST). *m*, the number of previously treated patients with both baseline and at least 1 postbaseline target lesion assessment.

Nearly 84% of patients with recurrent endometrial carcinoma have MSS or microsatellite-indeterminate tumors.¹⁵ Although pembrolizumab is effective for MSI-H disease (objective response, 28/49 [57.1%] patients),^{13,14} it appears less effective for MSS disease (best response was PR, 2/18 patients).¹⁶ Similarly, in advanced/recurrent previously treated endometrial carcinoma, investigational PD-1 monoclonal antibody dostarlimab (formerly TSR-042) had greater efficacy in patients with MSI-H tumors compared with patients with MSS tumors (ORR, [confirmed and unconfirmed responses] 50.0% and 19.1%, respectively).³⁰ ORRs observed with other investigational PD-L1 monoclonal antibodies have had similar trends in previously treated endometrial cancer (avelumab: 27%, patients with dMMR tumors; 6%, patients with pMMR tumors; durvalumab: 43%, patients with dMMR tumors; 3%, patients with pMMR tumors).^{31,32} Moreover, antiangiogenic and antimicrotubule medications have limited efficacy (ORR, 14%-16%; median PFS, 3.4-4.2 months) in recurrent/advanced endometrial carcinoma.^{33,34}

Our study had comparable results (ORR_{WK24}, 38.0%; ORR, 38.9%; median PFS, 7.4 months in patients with previously treated endometrial cancer) to the recently published interim analysis of lenvatinib plus pembrolizumab in endometrial cancer (ORR_{WK24}, 39.6%; ORR, 39.6%; median PFS, 7.4 months)²⁶ but with a longer follow-up time; as such, this suggests that the combination of lenvatinib plus pembrolizumab has favorable efficacy compared with that of previously reported therapies in similar populations.^{30,33,34} Importantly, tumor responses in our study were similar regardless of the tumor response criteria used and whether evaluated by investigator or IIR. Lenvatinib plus

pembrolizumab also demonstrated a robust depth of response; 84% of patients with evaluable tumor assessments had decreased tumor lesions (any size) from baseline, and 30% had a maximum decrease of $\geq 50\%$. Even more compelling, ORR in patients with difficult-to-treat MSS disease was 37.2%. Although the mechanistic basis for the encouraging efficacy of lenvatinib plus pembrolizumab in advanced endometrial carcinoma requires additional study, experimental models indicate lenvatinib modulates cancer immunity by decreasing the suppressive tumor-associated macrophage population,^{22,35} which may allow T cells reinvigorated by pembrolizumab to have enhanced antitumor activity.

The safety profile of lenvatinib plus pembrolizumab was generally similar to previously reported profiles of each monotherapy (lenvatinib, 24 mg/d; pembrolizumab, 10 mg/kg every 2 or 3 weeks).^{13,14,16,21,36-38} Although hypothyroidism occurred in a greater proportion of patients in our study than in previous reports of either monotherapy (48% [treatment-related, 43%] $v \leq 37\%$, respectively),^{36,37} there was only 1 occurrence of grade 3 hypothyroidism. Overall, the rate of grade 3/4 treatment-related AEs was similar in our study to the interim analysis of lenvatinib plus pembrolizumab in endometrial cancer (67% v 68%, respectively).²⁶ Timely identification of treatment-related AEs and their management throughout this study with dose interruptions and reductions may have facilitated treatment continuation, as only 17.7% of patients discontinued study treatment(s) because of treatment-related AEs. On average, patients received 11 pembrolizumab treatments, with only 4 patients reaching the maximum number of allowable doses ($n = 3, 35$

TABLE 3. Treatment-Related Adverse Events (\geq 20% any grade or any grade 3 or grade 4 events)

Preferred Term or Basket	Previously Treated EC ^a (n = 108)		All EC (N = 124)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Patients with any treatment-related TEAEs	105 (97.2)	75 (69.4)	120 (96.8)	83 (66.9)
Hypertension ^b	66 (61.1)	35 (32.4)	74 (59.7)	39 (31.5)
Diarrhea	57 (52.8)	7 (6.5)	65 (52.4)	8 (6.5)
Fatigue	56 (51.9)	9 (8.3)	59 (47.6)	9 (7.3)
Decreased appetite	51 (47.2)	0	59 (47.6)	0
Hypothyroidism ^c	48 (44.4)	1 (0.9)	54 (43.5)	1 (0.8)
Nausea	43 (39.8)	3 (2.8)	48 (38.7)	3 (2.4)
Stomatitis	36 (33.3)	0	39 (31.5)	0
Pain and arthralgia ^d	34 (31.5)	2 (1.9)	37 (29.8)	2 (1.6)
Dysphonia	30 (27.8)	0	34 (27.4)	0
PPE and severe skin reactions ^e	29 (26.9)	5 (4.6)	32 (25.8)	6 (4.8)
Vomiting	29 (26.9)	0	31 (25.0)	0
Weight decreased	28 (25.9)	2 (1.9)	30 (24.2)	2 (1.6)
Proteinuria ^f	24 (22.2)	4 (3.7)	30 (24.2)	4 (3.2)
Headache	22 (20.4)	0	25 (20.2)	0
Myalgia	19 (17.6)	1 (0.9)	20 (16.1)	1 (0.8)
Hepatotoxicity and hepatitis ^g	16 (14.8)	3 (2.8)	21 (16.9)	4 (3.2)
Hypomagnesemia	16 (14.8)	2 (1.9)	18 (14.5)	2 (1.6)
Abdominal pain and upper abdominal pain ^h	15 (13.9)	2 (1.9)	17 (13.7)	2 (1.6)
Asthenia	14 (13.0)	6 (5.6)	19 (15.3)	7 (5.6)
Hemorrhage ⁱ	14 (13.0)	3 (2.8)	19 (15.3)	4 (3.2)
Lipase increased	12 (11.1)	7 (6.5)	13 (10.5)	7 (5.6)
QT prolongation and cardiac dysfunction ^j	10 (9.3)	2 (1.9)	10 (8.1)	2 (1.6)
Dehydration	9 (8.3)	1 (0.9)	9 (7.3)	1 (0.8)
Renal events and nephritis ^k	9 (8.3)	2 (1.9)	9 (7.3)	2 (1.6)
Dyspnea	8 (7.4)	1 (0.9)	8 (6.5)	1 (0.8)
Oral pain	8 (7.4)	1 (0.9)	8 (6.5)	1 (0.8)
Confusional state and delirium ^l	7 (6.5)	4 (3.7)	7 (5.6)	4 (3.2)
Hyponatremia	7 (6.5)	5 (4.6)	7 (5.6)	5 (4.0)
Hypokalemia	5 (4.6)	1 (0.9)	6 (4.8)	2 (1.6)
Anemia	5 (4.6)	1 (0.9)	5 (4.0)	1 (0.8)
Adrenal insufficiency ^m	4 (3.7)	3 (2.8)	4 (3.2)	3 (2.4)
Amylase increased	4 (3.7)	2 (1.9)	4 (3.2)	2 (1.6)
Colitis ⁿ	4 (3.7)	2 (1.9)	4 (3.2)	2 (1.6)
Pancreatitis ^o	4 (3.7)	1 (0.9)	4 (3.2)	1 (0.8)
Pulmonary embolism	4 (3.7)	4 (3.7)	4 (3.2)	4 (3.2)
Hypotension	3 (2.8)	1 (0.9)	3 (2.4)	1 (0.8)
Syncope	3 (2.8)	2 (1.9)	3 (2.4)	2 (1.6)
Hypertriglyceridemia	2 (1.9)	0	3 (2.4)	1 (0.8)
Arterial TE events ^p	2 (1.9)	1 (0.9)	2 (1.6)	1 (0.8)
Colitis ischemic	2 (1.9)	2 (1.9)	2 (1.6)	2 (1.6)
Hyperkalemia	2 (1.9)	1 (0.9)	2 (1.6)	1 (0.8)

(continued on following page)

TABLE 3. Treatment-Related Adverse Events ($\geq 20\%$ any grade or any grade 3 or grade 4 events) (continued)

Preferred Term or Basket	Previously Treated EC ^a (n = 108)		All EC (N = 124)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Small intestinal obstruction	2 (1.9)	1 (0.9)	2 (1.6)	1 (0.8)
GI perforation ^q	1 (0.9)	1 (0.9)	2 (1.6)	2 (1.6)
Cholecystitis acute	1 (0.9)	1 (0.9)	1 (0.8)	1 (0.8)
Dysarthria	1 (0.9)	1 (0.9)	1 (0.8)	1 (0.8)
<i>Escherichia</i> sepsis	1 (0.9)	1 (0.9)	1 (0.8)	1 (0.8)
Hypocalcemia ^f	1 (0.9)	1 (0.9)	1 (0.8)	1 (0.8)
Hypophysitis ^s	1 (0.9)	1 (0.9)	1 (0.8)	1 (0.8)
Neutropenia	1 (0.9)	1 (0.9)	1 (0.8)	1 (0.8)
Pelvic abscess	1 (0.9)	1 (0.9)	1 (0.8)	1 (0.8)
Pneumothorax	1 (0.9)	1 (0.9)	1 (0.8)	1 (0.8)
Rectal ulcer	1 (0.9)	1 (0.9)	1 (0.8)	1 (0.8)

NOTE. Data are presented as No. (%). Patients are counted in the worst grade experienced of grade 3 or 4.

Abbreviations: AE, adverse event; EC, endometrial carcinoma; PPE, palmar-plantar erythrodysesthesia; TE, thromboembolism; TEAEs, treatment-emergent adverse events.

^aEnrolled before July 1, 2018.

^bHypertension basket (preferred terms: hypertensive encephalopathy, essential hypertension, hypertension).

^cHypothyroidism basket (preferred terms: hypothyroidism and blood thyroid-stimulating hormone increased).

^dCombines 2 preferred terms: pain and arthralgia.

^eCombines PPE basket (preferred term: PPE syndrome) with severe skin reactions basket (preferred terms: exfoliative rash, rash maculopapular, rash pruritic).

^fProteinuria basket (preferred term: proteinuria).

^gCombines hepatotoxicity basket (preferred terms: ascites, autoimmune hepatitis, hepatitis, hyperbilirubinemia, jaundice, alanine aminotransferase increase, AST increased, blood alkaline phosphatase increased, blood bilirubin increased, transaminases increased, hypoalbuminemia, encephalopathy, metabolic encephalopathy) and hepatitis basket (preferred terms: autoimmune hepatitis and hepatitis).

^hCombines 2 preferred terms: abdominal pain and upper abdominal pain.

ⁱHemorrhage basket term (preferred terms: GI hemorrhage, gingival bleeding, hematemesis, hematochezia, large intestinal hemorrhage, mouth hemorrhage, upper GI hemorrhage, catheter site bruise, injection site hemorrhage, contusion, hemorrhage intracranial, intraventricular hemorrhage, hematuria, coital bleeding, metrorrhagia, uterine hemorrhage, vaginal hemorrhage, epistaxis, hematoma).

^jQT prolongation basket (preferred term: electrocardiogram QT prolonged).

^kCombines renal events basket (preferred term: blood creatinine increased, acute kidney injury, nephritis, renal failure, renal vein thrombosis) and nephritis basket (preferred term: autoimmune nephritis, nephritis).

^lCombines 2 preferred terms: confusional state and delirium.

^mAdrenal insufficiency basket (preferred term: adrenal insufficiency).

ⁿColitis basket (preferred term: colitis).

^oPancreatitis basket (preferred terms: pancreatitis, pancreatitis acute).

^pArterial TE events basket (preferred terms: cerebral ischemia, ischemic cerebral infarction, transient ischemic attack).

^qGI perforation basket (preferred terms: gastric perforation, GI perforation, large intestine perforation, abdominal abscess).

^rHypocalcemia basket (preferred term: hypocalcemia).

^sHypophysitis basket (preferred term: hypopituitarism).

treatments; and n = 1, 36 treatments [allowable before protocol amendment 4]).

This study is limited by its nonrandomized nature. Moreover, exploratory analyses regarding PD-L1 status should be viewed with caution, as the cutoff for PD-L1 positivity is not definitive, and it is not known if PD-L1 status is a positive prognostic indicator in endometrial cancer. Additional limitations include the absence of a quality-of-life analysis as well as a lack of biomarker assessments to characterize patients susceptible to checkpoint inhibitors (ie, tumor mutational burden and mutation-associated neoantigens);

however, biomarker analyses are planned. It should be noted that although this trial may be considered small, its size (key efficacy analysis, n = 108; overall population, n = 124) is comparable to the collective size of trials that led to the approval of pembrolizumab in patients with MSI-H cancers (n = 149).³⁹

Overall, the results of this study are encouraging and showed compelling efficacy and an acceptable safety profile in patients with advanced endometrial carcinoma. As a result of this study, lenvatinib plus pembrolizumab was granted accelerated approval for the treatment of patients

with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression after prior systemic therapy, and who are not candidates for curative surgery or radiation.⁴⁰ In addition, two phase III trials of lenvatinib plus pembrolizumab in advanced endometrial

carcinoma are currently underway (ClinicalTrials.gov identifier: [NCT03884101](https://clinicaltrials.gov/ct2/show/study/NCT03884101) [v carboplatin plus paclitaxel in the first-line setting] and ClinicalTrials.gov identifier: [NCT03517449](https://clinicaltrials.gov/ct2/show/study/NCT03517449) [v doxorubicin or paclitaxel in previously treated patients]).

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CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer**

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Consulting or Advisory Role: Bayer, AstraZeneca, Eisai, Blueprint Medicines, Loxo, Novartis, Genzyme, Bristol-Myers Squibb

Research Funding: Bayer (Inst), Eisai (Inst), Novartis (Inst), Roche/Genentech (Inst), Exelixis (Inst), Blueprint Medicines (Inst), Loxo (Inst)

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Corina E. Dutcus

Employment: Eisai

Jane Wu

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Emmett V. Schmidt

Employment: Merck Sharp & Dohme

Stock and Other Ownership Interests: Merck Sharp & Dohme

Travel, Accommodations, Expenses: Merck Sharp & Dohme

Robert Orlowski

Employment: Merck Sharp & Dohme

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Research Funding: Merck Sharp & Dohme

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Employment: Eisai

Travel, Accommodations, Expenses: Eisai, Eisai

Robert Shumaker

Employment: Eisai

Employment: RRD International (I)

Antonio Casado Herraes

Consulting or Advisory Role: Roche Spain, PharmaMar, Eisai, Merck Sharp & Dohme

Research Funding: PharmaMar (Inst)

Travel, Accommodations, Expenses: PharmaMar, Roche, Lilly Spain

Other Relationship: Lilly (Inst)

No other potential conflicts of interest were reported.