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A Phase Ib/II Study of Lenvatinib and Pembrolizumab in Advanced Endometrial Carcinoma (Study 111/KEYNOTE-146): Long-Term Efficacy and Safety Update.

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A Phase Ib/II Study of Lenvatinib and Pembrolizumab in Advanced Endometrial Carcinoma (Study 111/KEYNOTE-146): Long-Term Efficacy and Safety Update

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abstract

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

The open-label phase Ib/II Study 111/KEYNOTE-146 of daily lenvatinib 20 mg plus pembrolizumab 200 mg once every 3 weeks showed promising efficacy and tolerable safety in patients with previously treated advanced endometrial carcinoma (EC; primary data cutoff date: January 10, 2019). This updated analysis reports long-term follow-up efficacy and safety data from 108 patients with previously treated EC included in the primary analysis. End points included objective response rate, duration of response, progression-free survival, overall survival, and safety. Investigators performed tumor assessments per immune-related RECIST. At the updated data cutoff date (August 18, 2020), the median study follow-up duration was 34.7 months (95% CI, 30.9 to 41.2), the objective response rate was 39.8% (95% CI, 30.5 to 49.7), and the median duration of response was 22.9 months (95% CI, 10.2 to not estimable). The median progression-free survival and overall survival were 7.4 months (95% CI, 5.2 to 8.7) and 17.7 months (95% CI, 15.5 to 25.8), respectively. Treatment-related treatment-emergent adverse events of any grade occurred in 104 (96.3%) patients. The most common grade ≥ 3 treatment-related treatment-emergent adverse events were hypertension (33.3%), elevated lipase (9.3%), fatigue (8.3%), and diarrhea (7.4%). The results demonstrate extended efficacy and tolerability of lenvatinib plus pembrolizumab in this cohort of patients with previously treated advanced EC.

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INTRODUCTION

Endometrial carcinoma (EC), the most common gynecologic cancer in the United States,[1] has a 5-year relative survival rate of 20% in patients with distant metastases.[2] Lenvatinib (an oral multikinase inhibitor of vascular endothelial growth factor receptors 1-3, fibroblast growth factor receptors 1-4, platelet-derived growth factor receptor α, RET, and KIT[3-6]) is approved in the United States and Canada in combination with pembrolizumab (an anti–programmed death receptor-1 monoclonal antibody[7]) for the treatment of patients with advanced EC that is not microsatellite instability-high (MSI-H) or mismatch-repair deficient (dMMR) who have disease progression after prior systemic (the United States) or platinum-based systemic (Canada) therapy and are not candidates for curative surgery or radiation.[8-11] The combination is also approved in Europe for treating patients with advanced EC who have disease progression after platinum-containing therapy and are not candidates for curative surgery or radiation.[12,13]

The phase III Study 309/KEYNOTE-775 demonstrated significantly longer progression-free survival (PFS) and overall survival (OS) with lenvatinib plus pembrolizumab versus the physician's choice of chemotherapy in patients (intention-to-treat population and patients with mismatch-repair proficient [pMMR] tumors) with previously treated advanced endometrial cancer.[14] The earlier open-label, single-arm, phase Ib/II Study 111/KEYNOTE-146 (ClinicalTrials.gov identifier: NCT02501096), which evaluated lenvatinib plus pembrolizumab in patients with previously treated advanced EC (primary analysis data cutoff date: January 10, 2019) showed promising efficacy and a tolerable safety profile,

ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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TABLE 1. Baseline Demographic and Clinical Characteristics

Parameter	Total (n = 108)[a]	Non–MSI-H/pMMR (n = 94)	MSI-H/dMMR (n = 11)
Age, years, mean (SD)	65.1 (7.60)	65.4 (7.42)	62.4 (9.45)
Race, No. (%)			
White	93 (86.1)	81 (86.2)	9 (81.8)
Black or African American	6 (5.6)	6 (6.4)	0
Asian	5 (4.6)	4 (4.3)	1 (9.1)
American Indian or Alaskan Native	1 (0.9)	1 (1.1)	0
Native Hawaiian or other Pacific Islander	1 (0.9)	0	1 (9.1)
Other	2 (1.9)	2 (2.1)	0
ECOG PS, No. (%)			
0	53 (49.1)	49 (52.1)	1 (9.1)
1	55 (50.9)	45 (47.9)	10 (90.9)
Histological subtype, No. (%)			
Endometrioid adenocarcinoma	55 (50.9)	46 (48.9)	8 (72.7)
FIGO grade 1	12 (11.1)	10 (10.6)	2 (18.2)
FIGO grade 2	19 (17.6)	15 (16.0)	4 (36.4)
FIGO grade 3	24 (22.2)	21 (22.3)	2 (18.2)
Serous adenocarcinoma	35 (32.4)	33 (35.1)	0
Clear cell adenocarcinoma	6 (5.6)	5 (5.3)	1 (9.1)
Dedifferentiated/undifferentiated carcinoma	1 (0.9)	0	1 (9.1)
Adenocarcinoma, not otherwise specified	1 (0.9)	1 (1.1)	0
Other[b]	10 (9.3)	9 (9.6)	1 (9.1)
PD-L1 status,[c] No. (%)			
Positive	53 (49.1)	46 (48.9)	7 (63.6)
Negative	43 (39.8)	39 (41.5)	4 (36.4)
Not available	12 (11.1)	9 (9.6)	0
Prior treatment regimens, No. (%)[d]			
1	56 (51.9)	47 (50.0)	7 (63.6)
≥ 2	52 (48.1)	47 (50.0)	4 (36.4)
Previous platinum plus taxane combination for EC,[e] No. (%)	106 (98.1)	92 (97.9)	11 (100.0)

NOTE. A subset of data shown in this table was adapted from Makker V, Taylor MH, Aghajanian C, et al: Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer. *Journal of Clinical Oncology*, volume 38, issue 26, pp. 2981-2992, 2020.[15]

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; PD-L1, programmed death ligand-1; pMMR, mismatch-repair proficient; SD, standard deviation.

[a]The microsatellite instability or mismatch-repair status was not available for three patients.

[b]Predominantly mixed histology.

[c]PD-L1 status is positive if CPS is ≥ 1 and negative if CPS is < 1; PD-L1 status was considered unknown for patients for whom no status is reported.

[d]Eleven patients received > 2 prior systemic therapies. Hormonal therapies were considered to be a separate line of therapy (a total of 13 of the 108 patients received prior hormonal therapy).

[e]With or without other anticancer medication.

irrespective of mismatch-repair (MMR) status.[15] The objective response rate (ORR) by investigators per immune-related RECIST (irRECIST)[16] was 38.9% (95% CI, 29.7 to 48.7); the median duration of response (DOR) was 21.2 months (95% CI, 7.6 to not estimable [NE]). PFS by investigator assessment per irRECIST and OS were 7.4 months (95% CI, 5.3 to 8.7) and 16.7 months (95% CI, 15.0 to NE), respectively. Grade 3-4 treatment-related treatment-emergent adverse events (TEAEs) occurred in 69.4% of patients. To our knowledge, in this first extended follow-up analysis of lenvatinib plus pembrolizumab in patients with previously treated advanced EC, we report long-term efficacy and safety results from Study 111/KEYNOTE-146.

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TABLE 2. Summary of Efficacy End Points (investigator assessment per irRECIST)

	Patients With Previously Treated EC			
	Previous Data Cutoff Date: January 10, 2019[15]	Updated Data Cutoff Date: August 18, 2020[a]		
Investigator Assessment per irRECIST	Total (n = 108)	Total (n = 108)	Non–MSI-H/pMMR (n = 94)	MSI-H/dMMR (n = 11)
ORR, No. (%)	42 (38.9)	43 (39.8)	36 (38.3)	7 (63.6)
95% CI	29.7 to 48.7	30.5 to 49.7	28.5 to 48.9	30.8 to 89.1
Complete response, No. (%)	8 (7.4)	9 (8.3)[b]	8 (8.5)	1 (9.1)
Partial response, No. (%)	34 (31.5)	34 (31.5)	28 (29.8)	6 (54.5)
Stable disease, No. (%)	49 (45.4)	46 (42.6)	41 (43.6)	3 (27.3)
Durable stable disease rate,[c] No. (%)	21 (19.4)	18 (16.7)	17 (18.1)	1 (9.1)
Clinical benefit rate,[d] No. (%)	63 (58.3)	61 (56.5)	53 (56.4)	8 (72.7)
95% CI	48.5 to 67.7	46.6 to 66.0	45.8 to 66.6	39.0 to 94.0
Disease control rate,[e] No. (%)	91 (84.3)	89 (82.4)	77 (81.9)	10 (90.9)
95% CI	76.0 to 90.6	73.9 to 89.1	72.6 to 89.1	58.7 to 99.8
Median DOR, months (95% CI)[f]	21.2 (7.6 to NE)	22.9 (10.2 to NE)	23.0 (8.5 to NE)	21.2 (7.3 to NE)
No. of patients with DOR, probability, Kaplan-Meier estimate[g]				
≥ 6 months, No.	32	36	29	7
Probability (95% CI)	0.87 (0.72 to 0.95)	0.88 (0.73 to 0.95)	0.85 (0.68 to 0.94)	1.00 (NE to NE)
≥ 12 months, No.	12	25	21	4
Probability (95% CI)	0.63 (0.45 to 0.77)	0.65 (0.48 to 0.77)	0.64 (0.45 to 0.78)	0.67 (0.19 to 0.90)
Median PFS, months (95% CI)[h]	7.4 (5.3 to 8.7)	7.4 (5.2 to 8.7)	7.4 (4.4 to 7.6)	26.4 (4.0 to NE)
Median OS, months (95% CI)[h]	16.7 (15.0 to NE)	17.7 (15.5 to 25.8)	17.2 (15.0 to 25.8)	NE (7.4 to NE)
Time to response, months, mean (SD)	2.6 (1.6)	3.2 (3.41)[i]	3.2 (3.65)	2.9 (1.84)
Median study follow-up time, months (95% CI)	18.7 (13.1 to 20.3)	34.7 (30.9 to 41.2)	35.8 (31.2 to 41.2)	34.7 (20.5 to 59.3)

Abbreviations: dMMR, mismatch-repair deficient; DOR, duration of response; EC, endometrial carcinoma; irRECIST, immune-related RECIST; MSI-H, microsatellite instability-high; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pMMR, mismatch-repair proficient; SD, standard deviation.

[a]Two patients remained on lenvatinib plus pembrolizumab, and four patients remained on lenvatinib only at data cutoff date.

[b]Two patients with complete response (both were non–MSI-H/pMMR) experienced disease progression (both patients discontinued pembrolizumab and were receiving single-agent lenvatinib at the time of disease progression).

[c]Durable stable disease rate = proportion of patients with durable stable disease (duration of stable disease ≥ 23 weeks).

[d]Clinical benefit rate = proportion of complete response + partial response + durable stable disease (duration of stable disease ≥ 23 weeks).

[e]Disease control rate = proportion of complete response + partial response + stable disease (duration of stable disease ≥ 5 weeks).

[f]At the updated data cutoff date, DOR ranges were 1.2+ to 52.5+ months for all patients, 1.2+ to 52.5+ months for those with non–MSI-H/pMMR tumors, and 6.4+ to 50.3+ months for those with MSI-H/dMMR tumors.

[g]Probability and 95% CI are calculated using the Kaplan-Meier product-limit method and Greenwood's formula.

[h]The median is estimated using the Kaplan-Meier method, and the 95% CI is constructed with a generalized Brookmeyer and Crowley method.

[i]The increase in time to response is driven by two patients who converted from stable disease to partial response at the updated data cutoff date (the times to response for these patients were 7.49 months and 22.01 months).

METHODS

Study 111/KEYNOTE-146 procedures have been published.[15,17] Eligible patients were age 18 years and older with histologically confirmed advanced EC, an Eastern Cooperative Oncology Group performance status ≤ 1, and life expectancy ≥ 12 weeks. Patients received ≤ 2 prior systemic therapies (unless discussed with the sponsor). Patients received lenvatinib 20 mg orally once daily and pembrolizumab 200 mg intravenously once every 3 weeks in 3-week cycles. End points for the primary analysis included ORR at week 24 (primary end point) and ORR, DOR, PFS, OS, disease control rate, and clinical benefit rate (secondary end points). End points for this follow-up analysis included ORR, DOR, PFS, OS, and safety. Tumors were evaluated at baseline, every 6 weeks for the first 24 weeks, and every 9 weeks thereafter; in this analysis, all assessments were by investigators per irRECIST. All previously treated

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patients included in the efficacy analysis and analyzed at the primary data cutoff were included in this updated analysis (data cutoff date: August 18, 2020). Efficacy end points (assessed in all patients who entered the study treatment period) were reported for all patients, patients who were non–MSI-H/pMMR, and patients who were MSI-H/dMMR. Treatment-related TEAEs (assessed in patients who received any amount of study drug) were graded using the Common Terminology Criteria for Adverse Events version 4.03. This study was approved by each research site's institutional review board or ethics committee.

RESULTS

Patients

Baseline characteristics are summarized in Table 1. At the updated data cutoff date, 32 (29.6%) patients were on study treatment or in survival follow-up; the remaining 76 (70.4%) patients discontinued the study because of death (n = 71), consent withdrawal (n = 4), or other reason (n = 1). Six (5.6%) patients were on study treatment (either on both drugs or lenvatinib only). The median follow-up was 34.7 months (95% CI, 30.9 to 41.2).

Efficacy

All analyses were updated using the new cutoff date (August 18, 2020). An efficacy summary is presented in Table 2. The ORR was 39.8% (95% CI, 30.5 to 49.7), with nine complete responses and 34 partial responses. The median DOR was 22.9 months (95% CI, 10.2 to NE), with the upper range of DOR ongoing at 4 years (Table 2, Appendix Fig A1, online only). Tumor responses were observed regardless of histological subtype (Appendix Table A1, online only). Overall, median PFS and OS were 7.4 months (95% CI, 5.2 to 8.7) and 17.7 months (95% CI, 15.5 to 25.8), respectively (Appendix Figs A2 and A3, online only).

In patients with non–MSI-H/pMMR and MSI-H/dMMR tumors, the ORR was 38.3% and 63.6%, respectively (Table 2); the median DOR was 23.0 months (95% CI, 8.5 to NE) and 21.2 months (95% CI, 7.3 to NE), respectively. Upper ranges of DOR were ongoing at 4 years for both subgroups (Table 2, Appendix Fig A1). The median PFS in patients with non–MSI-H/pMMR and MSI-H/dMMR tumors was 7.4 months (95% CI, 4.4 to 7.6) and 26.4 months (95% CI, 4.0 to NE; Appendix Fig A2), respectively; the median OS was 17.2 months (95% CI, 15.0 to 25.8), and NE (95% CI, 7.4 to NE) in patients with non–MSI-H/pMMR and MSI-H/dMMR tumors, respectively (Appendix Fig A3).

Safety

In the overall population, the median dose intensity of lenvatinib was 13.84 mg once per day; the median number of pembrolizumab treatment cycles was 10. An overview of treatment-related TEAEs is presented in Table 3. Any-grade treatment-related TEAEs occurred in 104 (96.3%) patients. Grade ≤ 3 and grade ≥ 4 treatment-related TEAEs occurred in 94 (87.0%) and 10 (9.3%) patients. Serious treatment-related TEAEs occurred in 35 (32.4%) patients (hypertension was the most common serious treatment-related TEAE [6.5% of patients]). Treatment-related TEAEs led to discontinuation of at least one study drug in 23 (21.3%) patients, discontinuation of both study drugs in

TABLE 3. Overview of Treatment-Related TEAEs

Parameter[a]	Patients With Previously Treated EC (n = 108), No. (%)
Patients with any treatment-related TEAEs	104 (96.3)[b]
Patients with any treatment-related serious TEAEs[c]	35 (32.4)
Patients with treatment-related TEAEs leading to study-drug discontinuation[d]	23 (21.3)
Both lenvatinib and pembrolizumab	9 (8.3)
Lenvatinib[e]	19 (17.6)
Pembrolizumab[f]	17 (15.7)
Patients with treatment-related TEAEs leading to study-drug dose reduction of lenvatinib	73 (67.6)
Patients with treatment-related TEAEs leading to study-drug interruption[d]	80 (74.1)
Both lenvatinib and pembrolizumab	34 (31.5)
Lenvatinib[e]	77 (71.3)
Pembrolizumab[f]	47 (43.5)

Abbreviations: EC, endometrial carcinoma; TEAE, treatment-emergent adverse event.

[a]Adverse events were coded using Medical Dictionary for Drug Regulatory Affairs version 23.0 and graded using the Common Terminology Criteria for Adverse Events version 4.03.

[b]Ninety-four (87.0%) and 10 (9.3%) patients experienced grade ≤ 3 and grade ≥ 4 treatment-related TEAEs, respectively.

[c]The most common treatment-related serious TEAEs were hypertension (occurring in 6.5% of patients), followed by adrenal insufficiency, confusional state, nausea, and transient ischemic attack (each occurring in 2.8% of patients).

[d]Drug action taken is for lenvatinib and/or pembrolizumab.

[e]Drug action taken for lenvatinib, regardless of the action taken for pembrolizumab.

[f]Drug action taken for pembrolizumab, regardless of the action taken for lenvatinib.

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nine (8.3%) patients, lenvatinib dose reductions in 73 (67.6%) patients, and interruption of one study drug or both study drugs in 80 (74.1%) patients. Any grade treatment-related TEAEs occurring in ≥ 20% of patients are shown in Appendix Table A2 (online only). The most common grade ≥ 3 treatment-related TEAEs were hypertension (33.3%), elevated lipase (9.3%), fatigue (8.3%), and diarrhea (7.4%). Aside from two treatment-related deaths reported in the primary analysis,[15] no additional treatment-related deaths occurred. Treatment-related serious TEAEs are presented in Appendix Table A3 (online only).

DISCUSSION

This follow-up analysis showed deep and durable tumor responses (with one additional complete response compared with the primary analysis[15]) in patients with previously treated advanced EC who received lenvatinib plus pembrolizumab. Tumor responses were observed regardless of histological subtype or MMR status. The combination continued to show compelling PFS and OS benefits in comparison with what would be expected on the basis of historical data for this treatment setting.[18,19] Lenvatinib plus pembrolizumab had a manageable safety profile that was generally comparable with established profiles of the individual monotherapies.[8,9,20-23]

Recently, a confirmatory phase III trial demonstrated significantly longer PFS (median 7.2 *v* 3.8 months; hazard ratio, 0.56; 95% CI, 0.47 to 0.66; $P < .001$) and OS (median 18.3 *v* 11.4 months; hazard ratio, 0.62; 95% CI, 0.51 to 0.75; $P < .001$) with lenvatinib plus pembrolizumab versus the physician's choice of chemotherapy in the intention-to-treat all-comer population of patients with previously treated advanced endometrial cancer (Study 309/KEYNOTE-775).[14] Treatment benefits were observed irrespective of MMR status. The extended follow-up of the phase II part of Study 111/KEYNOTE-146 provides data on the long-term efficacy and safety of this regimen. Although Study 111/KEYNOTE-146 was limited in that it was a single-arm study with a relatively small number of patients and enrollment sites, the results were confirmed in the randomized phase III global Study 309/KEYNOTE-775. The median PFS (7.4 months), median OS (17.7 months), and ORR (39.8%) in the overall population of Study 111/KEYNOTE-146 at extended follow-up were comparable with the efficacy findings of Study 309/KEYNOTE-775.[14] Similar to efficacy, safety results were also consistent with those of the primary analysis[15] and Study 309/KEYNOTE-775.[14] These results confirm the benefit of the combination in patients with previously treated advanced EC when lenvatinib is initiated at the recommended starting dose of 20 mg orally once daily (in combination with pembrolizumab 200 mg intravenously once every 3 weeks) and the individualized patient approach of dose interruption/modification or discontinuation is implemented.

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DATA SHARING STATEMENT

The data will not be available for sharing at this time because the data are commercially confidential. However, Eisai will consider written requests to share the data on a case-by-case basis.

AUTHOR CONTRIBUTIONS

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

A Phase Ib/II Study of Lenvatinib and Pembrolizumab in Advanced Endometrial Carcinoma (Study 111/KEYNOTE-146): Long-Term Efficacy and Safety Update

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APPENDIX 1.

Definitions of Efficacy End Points

Objective response rate is defined as the proportion of patients who had a best overall response of confirmed complete response or confirmed partial response at the time of data cutoff.

Duration of response (DOR) is defined as the time from the date of the first documentation of confirmed complete response or confirmed partial response (whichever occurred first) to the date of disease progression or death (whichever occurred first). Patients who had no record of disease progression or did not die before the data cutoff date were censored at the last available tumor assessment.

Clinical benefit rate is defined as the proportion of patients who had a best overall response of confirmed complete response, confirmed partial response, or durable confirmed stable disease (duration of confirmed stable disease ≥ 23 weeks).

Disease control rate is defined as the proportion of patients who had a best overall response of confirmed complete response, confirmed partial response, or confirmed stable disease (duration of confirmed stable disease ≥ 5 weeks).

Durable stable disease rate is defined as the proportion of patients whose best overall response was confirmed stable disease and the duration of confirmed stable disease was ≥ 23 weeks.

Progression-free survival is defined as the time from the first study dose date to the date of first documentation of confirmed disease progression or death (whichever occurred first). Patients who did not experience disease progression or death were censored at the date of the last available tumor assessment.

Overall survival is measured from the start date of the treatment period until date of death from any cause. Patients who were lost to follow-up and the patients who were alive at the date of data cutoff were censored at the date the patient was last known to be alive.

Statistical Methods

DOR: DOR among responders is defined as the time from the date that a confirmed response was first documented as the evidence of complete response or partial response until the date of the first documentation of disease progression or date of death from any cause, whichever occurs first. The median was estimated using the Kaplan-Meier method, and the 95% CI was constructed using a generalized Brookmeyer and Crowley method. All tumor assessments were considered, provided the patients did not start a new anticancer therapy.

Progression-free survival: The median was estimated using the Kaplan-Meier method, and the 95% CI was constructed using a generalized Brookmeyer and Crowley method. All tumor assessments were considered, provided the patients did not start a new anticancer therapy.

Overall survival: The median was estimated using the Kaplan-Meier method, and the 95% CI was constructed using a generalized Brookmeyer and Crowley method.

TABLE A1. Summary of Tumor Response by Histological Subtype (investigator assessment per irRECIST)

	Patients With Previously Treated EC (n = 108)			
Investigator Assessment per irRECIST	**Endometrioid Adenocarcinoma (n = 55)**	**Serous Adenocarcinoma (n = 35)**	**Clear Cell Adenocarcinoma (n = 6)**	**Other (n = 12)**
ORR, No. (%)	20 (36.4)	15 (42.9)	4 (66.7)	4 (33.3)
95% CI	23.8 to 50.4	26.3 to 60.6	22.3 to 95.7	9.9 to 65.1
CR, No. (%)	2 (3.6)	4 (11.4)	3 (50.0)	0
PR, No. (%)	18 (32.7)	11 (31.4)	1 (16.7)	4 (33.3)
CBR,[a] No. (%)	28 (50.9)	21 (60.0)	4 (66.7)	8 (66.7)
95% CI	37.1 to 64.6	42.1 to 76.1	22.3 to 95.7	34.9 to 90.1
Median DOR, months (95% CI)	21.2 (8.5 to NE)	20.9 (6.2 to 39.7)	NE (6.3 to NE)	14.7 (2.7 to 22.9)
Range, months	2.5+ to 52.5+	1.2+ to 39.7	6.3 to 39.4+	2.7 to 22.9
No. of patients with DOR, probability, Kaplan-Meier estimate[b]				
≥ 6 months, No.	17	12	4	3
Probability (95% CI)	0.89 (0.64 to 0.97)	0.86 (0.54 to 0.96)	1.00 (NE to NE)	0.75 (0.13 to 0.96)
≥ 12 months, No.	11	9	3	2
Probability (95% CI)	0.66 (0.39 to 0.83)	0.64 (0.34 to 0.83)	0.75 (0.13 to 0.96)	0.50 (0.06 to 0.84)

Abbreviations: CBR, clinical benefit rate; CR, complete response; DOR, duration of response; EC, endometrial carcinoma; irRECIST, immune-related RECIST; NE, not estimable; ORR, objective response rate; PR, partial response.

[a]CBR = proportion of CR + PR + durable stable disease (stable disease ≥ 23 weeks).

[b]Probability and 95% CI are calculated using the Kaplan-Meier product-limit method and Greenwood's formula.

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TABLE A2. Most Common (≥ 20% any grade) Treatment-Related TEAEs by Preferred Term[a]

	Severity of TEAEs in Patients With Previously Treated EC (n = 108)	
MedDRA Preferred Term	**Any Grade, No. (%)**	**Grade ≥ 3,[b] No. (%)**
Overall	104 (96.3)	77 (71.3)
Hypertension	65 (60.2)	36 (33.3)
Diarrhea	58 (53.7)	8 (7.4)
Fatigue	58 (53.7)	9 (8.3)
Decreased appetite	54 (50.0)	1 (0.9)
Hypothyroidism	50 (46.3)	1 (0.9)
Nausea	47 (43.5)	3 (2.8)
Stomatitis	39 (36.1)	0
Arthralgia	34 (31.5)	2 (1.9)
Vomiting	33 (30.6)	0
Weight decreased	32 (29.6)	2 (1.9)
Dysphonia	31 (28.7)	0
Palmar-plantar erythrodysesthesia syndrome	30 (27.8)	2 (1.9)
Proteinuria	29 (26.9)	4 (3.7)
Headache	25 (23.1)	0

Abbreviations: EC, endometrial carcinoma; MedDRA, Medical Dictionary for Drug Regulatory Affairs; TEAE, treatment-emergent adverse event.

[a]A patient with two or more adverse events with the same preferred term is counted only once for that preferred term. Treatment-related TEAEs include TEAEs that were considered by the investigator to be related to the study drug or TEAEs with a missing causality. Adverse events were coded using MedDRA version 23.0.

[b]Six patients had TEAEs with a fatal outcome (gastrointestinal perforation [n = 1], intestinal obstruction [n = 1], intestinal ulcer perforation [n = 1], sepsis [n = 1], *Escherichia* sepsis [n = 1], and hemorrhage intracranial [n = 1]).

TABLE A3. Treatment-Related Treatment-Emergent Serious Adverse Events (> 1% in all patients with EC)[a]

MedDRA Preferred Term	**Previously Treated EC (n = 108) Any Grade, No. (%)**
Patients with any treatment-related serious TEAEs	35 (32.4)
Hypertension	7 (6.5)
Adrenal insufficiency	3 (2.8)
Confusional state	3 (2.8)
Nausea	3 (2.8)
Transient ischemic attack	3 (2.8)
Asthenia	2 (1.9)
Colitis	2 (1.9)
Decreased appetite	2 (1.9)
Encephalopathy	2 (1.9)
Gastric perforation	2 (1.9)
Hyponatremia	2 (1.9)
Pancreatitis	2 (1.9)
Syncope	2 (1.9)

Abbreviations: EC, endometrial carcinoma; MedDRA, Medical Dictionary for Drug Regulatory Affairs; TEAE, treatment-emergent adverse event.

[a]A patient with two or more adverse events with the same preferred term is counted only once for that preferred term. Treatment-related TEAEs include TEAEs that were considered by the investigator to be related to the study drug or TEAEs with a missing causality. Adverse events were coded using MedDRA version 23.0.

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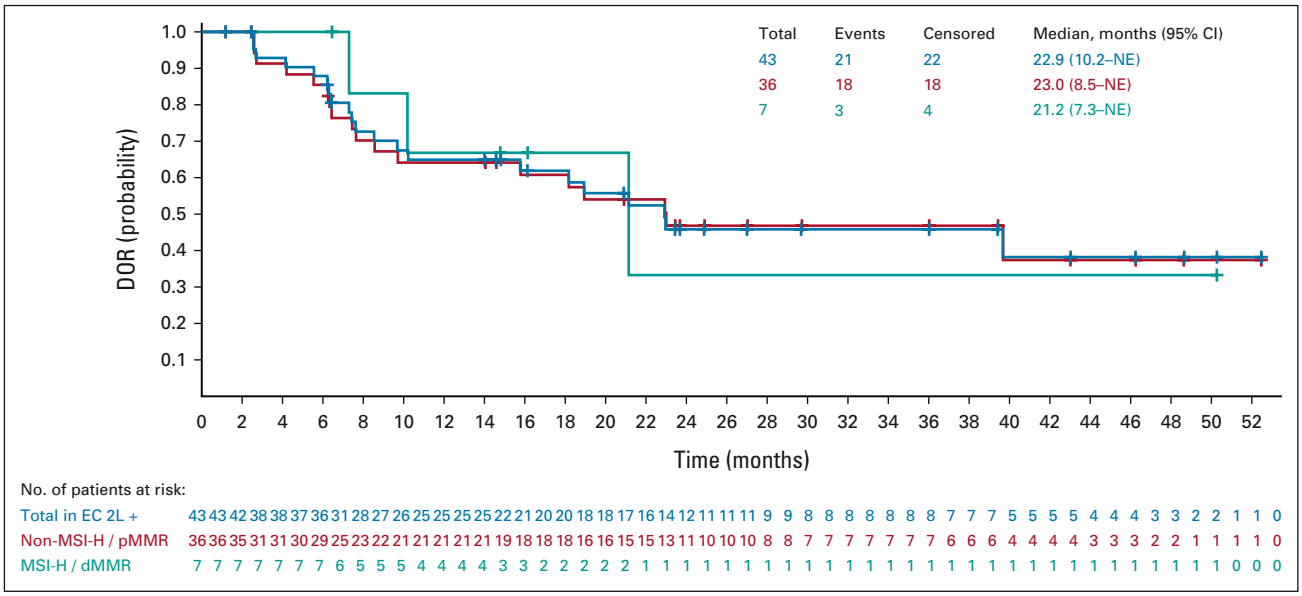

FIG A1. Kaplan-Meier plot of DOR (DOR among responders is defined as the time from the date that a confirmed response was first documented as the evidence of complete response or partial response until the date of the first documentation of disease progression or date of death from any cause, whichever occurs first; investigator assessment per irRECIST). The median was estimated using the Kaplan-Meier method, and the 95% CI was constructed using a generalized Brookmeyer and Crowley method. All tumor assessments were considered, provided the patients did not start a new anticancer therapy. Of the 22 patients in the overall population who were censored, 16 had no progression and no death at the time of data cutoff, three had death or progression after more than one missing assessment, and three had started a new anticancer treatment before radiological progression per irRECIST. 2L, second-line; dMMR, mismatch-repair deficient; DOR, duration of response; EC, endometrial carcinoma; irRECIST, immune-related RECIST; MSI-H, microsatellite instability-high; NE, not estimable; pMMR, mismatch-repair proficient.

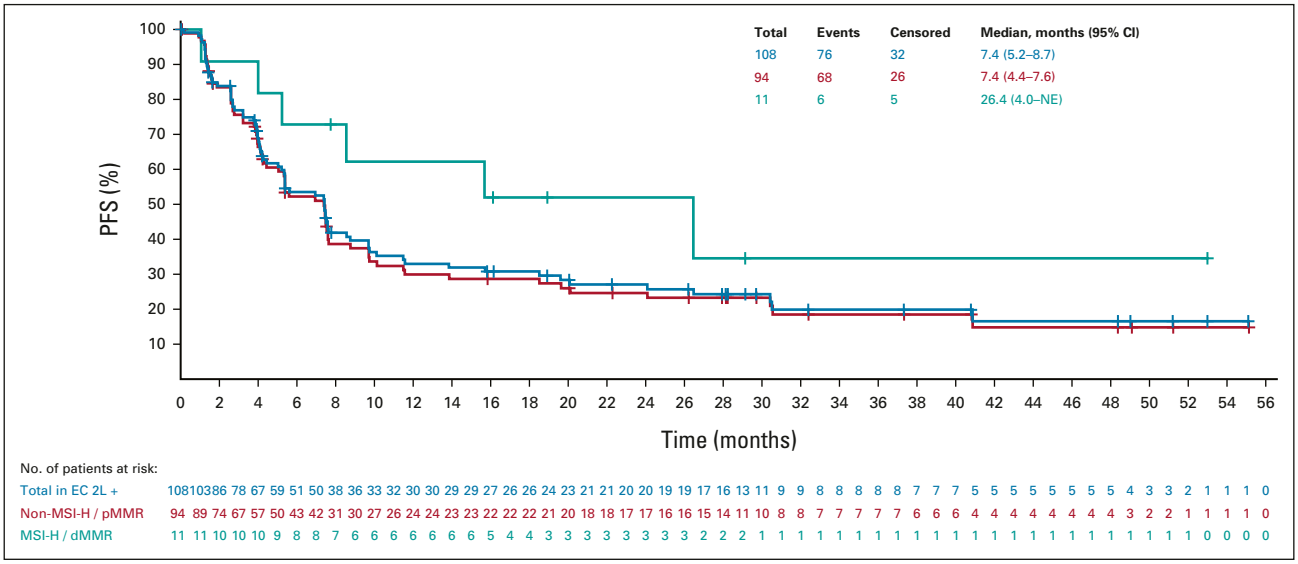

FIG A2. Kaplan-Meier plot of PFS (the median was estimated using the Kaplan-Meier method, and the 95% CI was constructed using a generalized Brookmeyer and Crowley method; investigator assessment per immune-related RECIST). All tumor assessments were considered, provided the patients did not start a new anticancer therapy. 2L, second-line; dMMR, mismatch-repair deficient; EC, endometrial carcinoma; MSI-H, microsatellite instability-high; NE, not estimable; PFS, progression-free survival; pMMR, mismatch-repair proficient.

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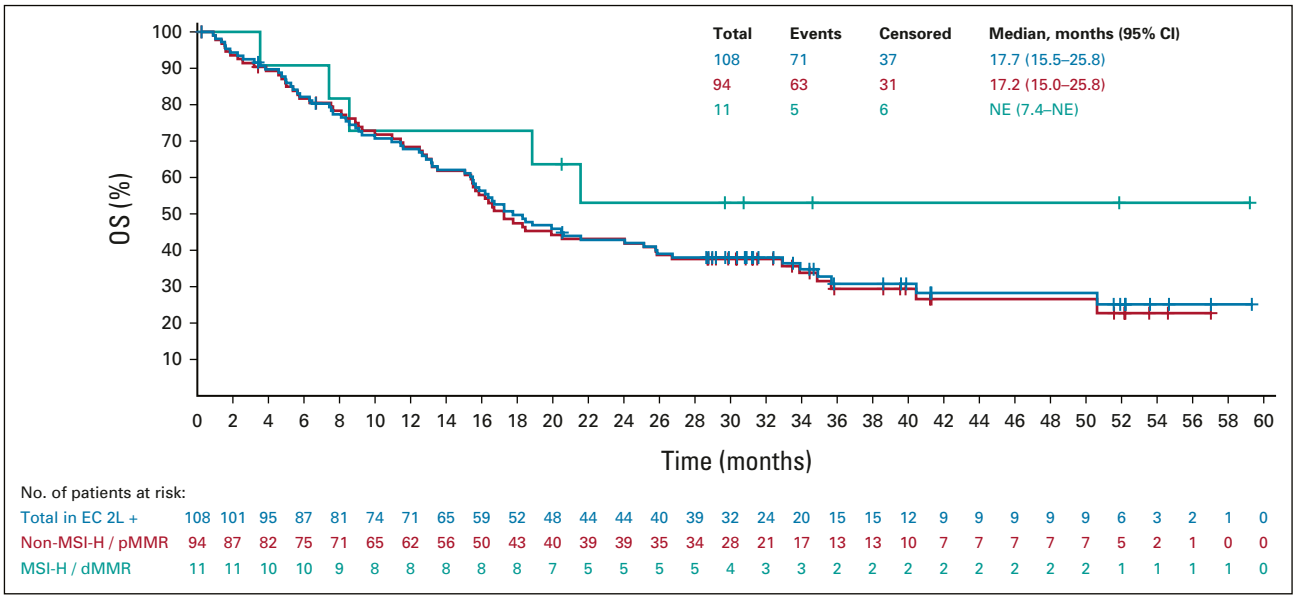

FIG A3. Kaplan-Meier plot of OS (the median was estimated using the Kaplan-Meier method, and the 95% CI was constructed using a generalized Brookmeyer and Crowley method). 2L, second-line; dMMR, mismatch-repair deficient; EC, endometrial carcinoma; MSI-H, microsatellite instability-high; NE, not estimable; OS, overall survival; pMMR, mismatch-repair proficient.

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