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Lenvatinib plus pembrolizumab in Japanese patients with endometrial cancer: Results from Study 309/KEYNOTE-775

Kan Yonemori[1] | Mayu Yunokawa[2] | Kimio Ushijima[3] | Jun Sakata[4] | Ayumi Shikama[5] | Shinichiro Minobe[6] | Tomoka Usami[7] | Takayuki Enomoto[8] | Kazuhiro Takehara[9] | Kosei Hasegawa[10] | Wataru Yamagami[11] | Keiko Yamamoto[12] | Shirong Han[12] | Lea Dutta[13] | Robert Orlowski[14] | Takuma Miura[15] | Vicky Makker[16] | Keiichi Fujiwara[10]

[1]National Cancer Center Hospital, Tokyo, Japan

[2]Cancer Institute Hospital of JFCR, Tokyo, Japan

[3]Kurume University Hospital, Fukuoka, Japan

[4]Aichi Cancer Center Hospital, Nagoya, Japan

[5]University of Tsukuba Hospital, Ibaraki, Japan

[6]Hokkaido Cancer Center, Sapporo, Japan

[7]Ehime University Hospital, Toon, Japan

[8]Niigata University Medical & Dental Hospital, Niigata, Japan

[9]National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan

[10]Saitama Medical University International Medical Center, Saitama, Japan

[11]Keio University Hospital, Tokyo, Japan

[12]MSD K.K., Tokyo, Japan

[13]Eisai Inc., Woodcliff Lake, New Jersey, USA

[14]Merck & Co., Inc., Rahway, New Jersey, USA

[15]Eisai Co., Ltd., Tokyo, Japan

[16]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical Center, New York, New York, USA

Correspondence
Kan Yonemori, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan.
Email: kyonemor@ncc.go.jp

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Abstract

Study 309/KEYNOTE-775 is a phase 3 open-label, randomized trial of lenvatinib plus pembrolizumab versus treatment of physician's choice (TPC) in patients with advanced endometrial cancer with progression after platinum-based therapy. Primary endpoints of superiority for lenvatinib plus pembrolizumab were met for progression-free survival (PFS) and overall survival (OS) in all-comers (ie, regardless of mismatch repair [MMR] status) and patients with MMR proficiency (pMMR). We present results for the Japanese subset. Patients were randomized to oral lenvatinib 20 mg/day plus intravenous pembrolizumab 200 mg every 3 weeks (Q3W; up to 35 cycles of pembrolizumab) or TPC (intravenous doxorubicin 60 mg/m^2 Q3W or paclitaxel 80 mg/m^2

Trial registration: ClinicalTrials.gov, NCT03517449

QW [3 weeks on/1 week off]). Primary endpoints were PFS by blinded independent central review per RECIST version 1.1 and OS. One hundred four patients were randomized in Japan (data cutoff, October 26, 2020; median follow-up, 11.8 [range, 1.1–26.9] months). Hazard ratios (HRs) for PFS with lenvatinib plus pembrolizumab versus TPC were 1.04 (95% CI, 0.63–1.73) in patients with pMMR and 0.81 (0.50–1.31) in all-comers. Hazard ratios for OS were 0.74 (0.41–1.34) with pMMR and 0.59 (0.33–1.04) for all-comers. Adverse events were manageable and led to discontinuation of one/both study drugs in 36.5% of patients in the lenvatinib plus pembrolizumab group versus 7.8% in the TPC group. Similar to the global Study 309/KEYNOTE-775 results, this analysis suggested favorable efficacy and manageable safety with lenvatinib plus pembrolizumab after platinum-based chemotherapy in Japanese patients with advanced endometrial cancer and supports this combination as a new standard of care in this population.

KEYWORDS
endometrial cancer, Japan, lenvatinib, pembrolizumab, treatment outcomes

1 | INTRODUCTION

The incidence of endometrial cancer in Japan has been steadily increasing, and it is now the most frequently diagnosed gynecologic cancer.[1] In 2014, approximately 20% of patients with endometrial cancer in Japan presented with locally advanced or metastatic disease. Based on data from regional cancer registrations between 1993 and 2011, 5-year overall survival (OS) in patients with stage IV disease was 20%.[2] The Japan Society of Gynecologic Oncology treatment guidelines include surgery, radiotherapy, or chemotherapy as recommended options for patients with advanced or recurrent endometrial cancer.[3] Many patients with disease recurrence have previously received chemotherapy and have limited subsequent treatment options.[3] Although immunotherapies are not included in the current treatment guidelines in Japan,[3] the anti–programmed death 1 (PD-1) monoclonal antibody pembrolizumab has been approved by the Japan Pharmaceuticals and Medical Devices Agency for unresectable or metastatic solid tumors with high microsatellite instability (MSI-H) that have progressed following prior treatment or for which there are no satisfactory alternative treatment options.[4]

Lenvatinib is a multitargeted tyrosine kinase inhibitor of vascular endothelial growth factor (VEGF) receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor α, RET, and KIT.[5] In preclinical studies, lenvatinib demonstrated immunomodulatory activity and increased antitumor activity when combined with anti–PD-1 therapy, supporting combination therapy with pembrolizumab.[6] This combination showed efficacy regardless of tumor MSI/mismatch repair (MMR) status in Study 111/KEYNOTE-146, a phase 1b/2, single-arm trial in patients with advanced endometrial cancer who had disease progression after systemic therapy.[7]

In the phase 3, randomized trial, Study 309/KEYNOTE-775 (ClinicalTrials.gov, NCT03517449),[8] significant improvements were demonstrated with lenvatinib in combination with pembrolizumab compared with treatment of physician's choice (TPC; doxorubicin or paclitaxel) in patients with advanced endometrial cancer and disease progression after prior systemic platinum-based therapy with respect to progression-free survival (PFS), OS, and objective response rate (ORR). Progression-free survival was significantly longer with lenvatinib plus pembrolizumab versus TPC in patients with MMR-proficient (pMMR) tumors (median PFS, 6.6 [95% CI, 5.6–7.4] months vs 3.8 [95% CI, 3.6–5.0] months; hazard ratio [HR], 0.60 [95% CI, 0.50–0.72]; $p < 0.001$) and in all-comers (median PFS, 7.2 [95% CI, 5.7–7.6] months vs 3.8 [95% CI, 3.6–4.2] months; HR, 0.56 [95% CI, 0.47–0.66]; $p < 0.001$). Overall survival also significantly favored lenvatinib plus pembrolizumab in those with pMMR tumors (median OS, 17.4 [95% CI, 14.2–19.9] months vs 12.0 [95% CI, 10.8–13.3] months; HR, 0.68 [95% CI, 0.56–0.84]; $p < 0.001$) and in all-comers (median OS, 18.3 [95% CI, 15.2–20.5] months vs 11.4 [95% CI, 10.5–12.9] months; HR, 0.62 [95% CI, 0.51–0.75]; $p < 0.001$).[8] The safety profile was consistent with the known profiles for each agent. We analyzed efficacy and safety results for Japanese patients enrolled in Study 309/KEYNOTE-775 to assess whether clinical outcomes in this group were consistent with those of the overall study population. Here we present results from the Japanese subset of patients enrolled in Study 309/KEYNOTE-775.

2 | MATERIALS AND METHODS

2.1 | Study design

Study 309/KEYNOTE-775 is a phase 3, multicenter, open-label, randomized trial evaluating the efficacy and safety of lenvatinib plus pembrolizumab versus TPC in patients with advanced endometrial cancer and disease progression after prior systemic platinum-based therapy. This study was conducted in accordance with the

International Council for Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki and was approved by institutional review boards or independent ethics committees at each site. All patients provided written informed consent.

2.2 | Patient eligibility

Patient eligibility for this study has been previously described.[8] Briefly, eligible patients were aged ≥18 years with confirmed advanced, recurrent, or metastatic endometrial cancer (excluding carcinosarcoma and sarcoma) and had disease progression after one prior platinum-based chemotherapy regimen, ≥1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, available tissue samples for evaluation of MMR status (see Assessments), and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. Patients could have received one additional line of prior platinum therapy if it was administered in the neoadjuvant/adjuvant setting. Patients were excluded if they had received any prior therapy targeting VEGF signaling, PD-1, programmed death ligand 1 (PD-L1), or PD-L2.

2.3 | Study treatment

Patients were randomly assigned in a 1:1 ratio to receive oral lenvatinib 20 mg/day plus intravenous (IV) pembrolizumab 200 mg every 3 weeks or to receive TPC (IV doxorubicin at 60 mg/m^2 every 3 weeks or IV paclitaxel at 80 mg/m^2 every week [3 weeks on/1 week off]). Randomization was stratified by MMR status; patients with pMMR tumors were further stratified by ECOG PS (0 vs 1), geographic region (Europe, USA, Canada, Australia, New Zealand, and Israel vs rest of the world), and history of pelvic radiation (yes vs no). Study treatment continued until disease progression, unacceptable toxicity, or, when applicable, completion of study treatment (administration of pembrolizumab for 35 cycles [2 years] or administration of a cumulative dose of 500 mg/m^2 of doxorubicin). Prespecified rules for dose interruption and/or modification are described in the protocol (Supplementary Material).

2.4 | Assessments

Tumor imaging was conducted at baseline, every 8 weeks until the primary analysis for the study, and then every 12 weeks thereafter. Response was assessed by blinded independent central review (BICR) per RECIST version 1.1. Adverse events (AEs) were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, and were monitored throughout the study and for 30 days (120 days for serious AEs) after treatment discontinuation.

Tumor tissue was collected from all enrolled patients for determination of MMR status by central assessment by pathologist evaluation before randomization. Mismatch repair was assessed in archived tumor tissue from the most recent surgery/biopsy or from a fresh biopsy if no archival tumor tissue was available. Automated immunohistochemistry staining and chromogenic labeling of the MMR proteins MLH1, MSH2, MSH6, and PMS2 on the Ventana Benchmark Ultra was performed using mouse and rabbit antibodies (Roche Diagnostics). Specifically, the MLH1 (clone M1, mouse monoclonal, Ventana, Cat# 790–5091), PMS2 (clone A16-4, mouse monoclonal, Ventana, Cat# 790–5094), MSH2 (clone G219-1129, mouse monoclonal, Ventana, Cat# 790–5093), and MSH6 (clone SP93, rabbit monoclonal, Ventana, Cat# 790–5092) antibodies were used to perform immunohistochemistry staining.

2.5 | Study endpoints

The primary endpoints were PFS by BICR per RECIST version 1.1 and OS. Secondary endpoints included ORR by BICR per RECIST version 1.1 and safety. Duration of response was a key exploratory endpoint. Efficacy endpoints in this analysis were assessed in all randomized patients enrolled in Japan (intent-to-treat [ITT] population) in the following subgroups according to MRR status: those with pMMR, all-comers (all patients regardless of MMR status), and patients with MMR deficiency (dMMR). Safety was assessed in all randomized patients who received ≥1 dose of study treatment (all patients as-treated population).

2.6 | Statistical analyses

The study was designed and powered to evaluate hypotheses in the global pMMR and all-comer populations and was not designed to test hypotheses in the Japanese subset. Therefore, this study lacks power for inferential purposes in the Japanese subset, and all *P* values are nominal and one-sided. Progression-free survival and OS were estimated using the nonparametric Kaplan-Meier method, and treatment differences were assessed by the stratified log-rank test. Hazard ratios were assessed using a Cox proportional hazard model with the Efron method of tie handling. Differences in ORR were compared using the Miettinen and Nurminen method.

3 | RESULTS

3.1 | Patients

Among the global ITT population of 827 patients, a total of 104 patients were randomized in Japan as of the data cutoff date of October 26, 2020 (lenvatinib plus pembrolizumab, $n = 52$; TPC, $n = 52$). In the lenvatinib plus pembrolizumab arm, 44 patients had pMMR and 8 patients had dMMR tumors; in the TPC arm, 47 patients had pMMR and 5 had dMMR tumors. One patient in the TPC arm withdrew consent after randomization and discontinued

from the study prior to receiving study treatment. A total of 34 patients in the lenvatinib plus pembrolizumab arm discontinued therapy (due to disease progression [*n* = 25], AE [*n* = 8], and patient withdrawal [*n* = 1]), and 18 patients were still ongoing at the data cutoff date. In the TPC arm, 19 patients completed therapy and 29 discontinued therapy (due to disease progression [*n* = 22], AE [*n* = 4], patient withdrawal [*n* = 2], and complete response [*n* = 1]); 3 were still ongoing at the data cutoff date. Baseline characteristics are displayed in Table 1 for all-comers and in Table S1 for patients with pMMR. The median follow-up in all-comers in the Japanese subgroup was 11.8 (range, 1.1–26.9) months. Median duration of treatment with lenvatinib plus pembrolizumab was 9.4 months (range, 1 day to 26.8 months) and with TPC was 3.9 months (range, 1 day to 25.8 months).

3.2 | Efficacy

Median PFS was 5.6 (95% CI, 3.7–7.6) months with lenvatinib plus pembrolizumab and 5.6 (95% CI, 3.7–9.2) months with TPC in patients with pMMR disease (HR, 1.04; 95% CI, 0.63–1.73; $p = 0.5646$; Figure 1A). In all-comers, median PFS was 7.2 (95% CI, 3.7–8.8) months and 5.4 (95% CI, 3.7–7.2) months, respectively (HR, 0.81; 95% CI, 0.50–1.31; $p = 0.1961$; Figure 1B). In patients with dMMR disease (lenvatinib plus pembrolizumab, *n* = 8; TPC, *n* = 5), median PFS was not reached (NR; 95% CI, 2.0 months–NR) with lenvatinib plus pembrolizumab and 3.7 (95% CI, 1.2–7.2) months with TPC (HR, 0.17; 95% CI, 0.03–0.91; $p = 0.0099$). At 6 months, the PFS rate was 71.4% with lenvatinib plus pembrolizumab and 20.0% with TPC among patients with dMMR disease.

TABLE 1 Demographics and baseline disease characteristics in all-comer patients (ITT population)

Characteristics	Lenvatinib + pembrolizumab *N* = 52	TPC *N* = 52
Median age (range), years	62.5 (36–76)	63.0 (37–77)
Age <65 years	33 (63.5)	33 (63.5)
MMR status		
pMMR	44 (84.6)	47 (90.4)
dMMR	8 (15.4)	5 (9.6)
ECOG performance status		
0	43 (82.7)	44 (84.6)
1	9 (17.3)	8 (15.4)
History of pelvic radiation	6 (11.5)	4 (7.7)
Histology of initial diagnosis		
Endometrioid carcinoma	37 (71.2)	31 (59.6)
High-grade	14 (26.9)	12 (23.1)
Low-grade	22 (42.3)	18 (34.6)
Not specified	1 (1.9)	1 (1.9)
Serous carcinoma	8 (15.4)	8 (15.4)
Mixed	3 (5.8)	3 (5.8)
Clear cell carcinoma	2 (3.8)	2 (3.8)
Neuroendocrine	1 (1.9)	0
Undifferentiated histology	1 (1.9)	1 (1.9)
High-grade mucinous carcinoma[a]	0	1 (1.9)
High-grade serous	0	6 (11.5)
Prior lines of systemic treatment[b]		
1 prior line	35 (67.3)	31 (59.6)
≥2 prior lines	17 (32.7)	21 (40.4)
Prior lines of platinum-based treatment		
1 prior line	37 (71.1)	32 (61.5)
2 prior lines	15 (28.9)	20 (38.5)
Prior neoadjuvant and/or adjuvant treatment	37 (71.1)	43 (82.7)

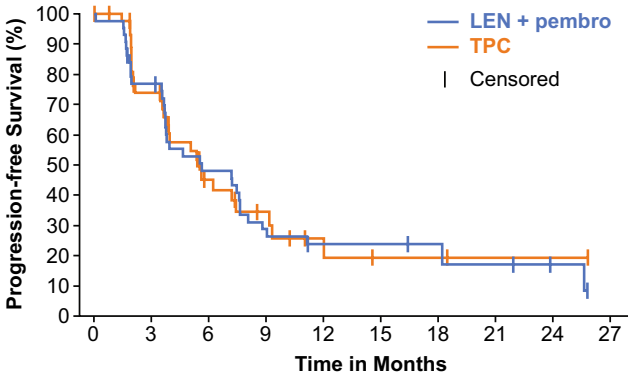
Note: Data are presented as *n* (%) unless specified otherwise.

Abbreviations: dMMR, mismatch repair-deficient; ECOG, Eastern Cooperative Oncology Group; ITT, intent to treat; pMMR, mismatch repair-proficient; TPC, treatment of physician's choice (doxorubicin or paclitaxel).

[a]There were no patients with low-grade mucinous carcinoma in either treatment group.

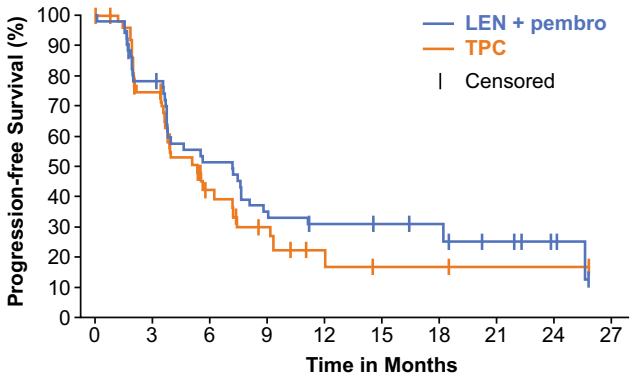
[b]Forty-three patients in the lenvatinib plus pembrolizumab arm and 36 patients in the TPC arm had received prior carboplatin and paclitaxel.

(A) Progression-free survival in pMMR patients



	44 33 20 12 8 8 7 5 2 0	
	47 29 13 8 4 2 2 1 1 0	
Median, mos (95% CI)	5.6 (3.7–7.6)	5.6 (3.7–9.2)
Events	35	27
HR (95% CI), *P*-value[a]	1.04 (0.63–1.73), *P* = 0.5646	

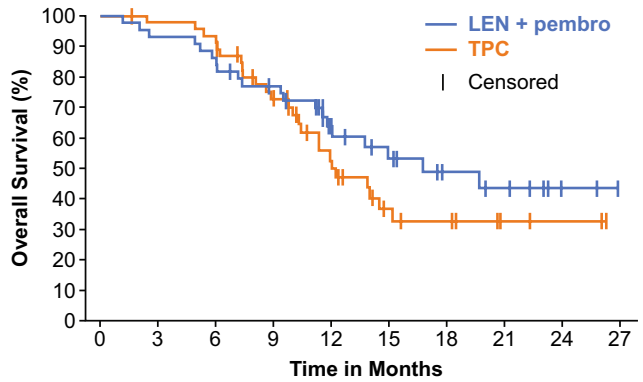
(B) Progression-free survival in all-comer patients



	52 39 25 17 13 12 11 7 3 0	
	52 33 14 8 4 2 2 1 1 0	
Median, mos (95% CI)	7.2 (3.7–8.8)	5.4 (3.7–7.2)
Events	37	32
HR (95% CI), *P*-value[a]	0.81 (0.50–1.31), *P* = 0.1961	

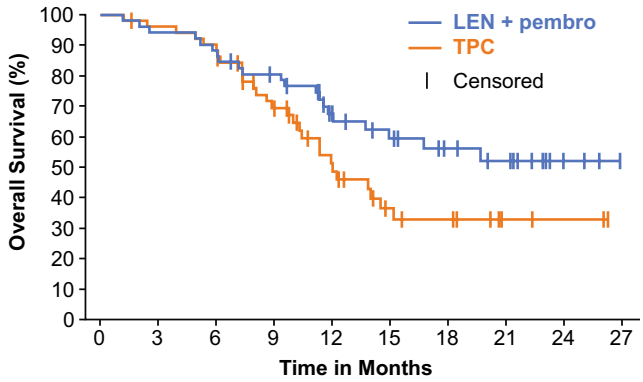
FIGURE 1 Progression-free survival in (A) pMMR patients and (B) all-comer patients. [a]All *P* values for the Japanese population should be considered nominal. HR, hazard ratio; len, lenvatinib; pembro, pembrolizumab; pMMR, mismatch repair-proficient; TPC, treatment of physician's choice (doxorubicin or paclitaxel)

(A) Overall survival in pMMR patients



	44 41 38 32 19 14 9 7 2 0	
	47 45 43 30 18 9 7 3 2 0	
Median, mos (95% CI)	16.7 (11.8–NR)	12.2 (10.3–15.2)
Events	20	25
HR (95% CI), *P*-value[a]	0.74 (0.41–1.34), *P* = 0.1610	

(B) Overall survival in all-comer patients



	52 49 46 40 26 21 15 12 3 0	
	52 49 46 32 19 10 8 3 2 0	
Median, mos (95% CI)	NR (12.1–NR)	12.0 (10.0–15.2)
Events	21	28
HR (95% CI), *P*-value[a]	0.59 (0.33–1.04), *P* = 0.0314	

FIGURE 2 Overall survival in (A) pMMR patients and (B) all-comer patients. [a]All *P* values for the Japanese population should be considered nominal. HR, hazard ratio; len, lenvatinib; NR, not reached; pembro, pembrolizumab; pMMR, mismatch repair-proficient; TPC, treatment of physician's choice (doxorubicin or paclitaxel)

Median OS was 16.7 (95% CI, 11.8–NR) months with lenvatinib plus pembrolizumab and 12.2 (95% CI, 10.3–15.2) months with TPC in patients with pMMR disease (HR, 0.74; 95% CI, 0.41–1.34; $p = 0.1610$; Figure 2A). In all-comers, median OS was NR (95% CI, 12.1 months–NR) and 12.0 (95% CI, 10.0–15.2) months, respectively (HR, 0.59; 95% CI, 0.33–1.04; $p = 0.0314$; Figure 2B). In patients with dMMR disease, the median OS was NR (95% CI, 11.3 months–NR; $n = 8$) with lenvatinib plus pembrolizumab and 8.0 (95% CI, 1.2–NR; $n = 5$) months with TPC (HR, 0.11; 95% CI, 0.01–1.13; $p = 0.0145$). At 12 months, the OS rate was 87.5% with lenvatinib plus pembrolizumab and 40.0% with TPC.

In patients with pMMR disease, the ORR was 31.8% (95% CI, 18.6%–47.6%) with lenvatinib plus pembrolizumab and 29.8% (95% CI, 17.3%–44.9%) with TPC (treatment difference, 2.0%; $p = 0.4174$). Median time to response was 2.1 (range, 1.7–3.9) months and 2.0 (range, 1.7–7.4) months, and median duration of response was 23.7 (range, 1.6 to 23.7+) months and 5.2 (range, 2.1+ to 24.2+) months, respectively. In all-comers, the ORR was 36.5% (95% CI, 23.6%–51.0%) with lenvatinib plus pembrolizumab and 26.9% (95% CI, 15.6%–41.0%) with TPC (treatment difference, 9.6%; $p = 0.1472$). Median time to response was 2.1 (range, 1.7–5.6) months and 2.0 (range, 1.7–7.4) months, and median duration

of response was 23.7 (range, 1.6 to 23.7+) months and 5.2 (range, 2.1+ to 24.2+) months, respectively (Table 2). In patients with dMMR disease, the ORR was 62.5% (95% CI, 24.5%–91.5%) among the eight patients who received lenvatinib plus pembrolizumab, whereas none of the five patients who received TPC experienced a response (treatment difference, 62.5%; $p = 0.0152$). Among patients with dMMR disease, median time to response with lenvatinib plus pembrolizumab was 3.9 (range, 1.9–5.6) months and median duration of response was NR (range, 9.0+ to 20.4+ months).

3.3 | Safety

All patients experienced ≥1 AE (Table 3). Grade 3 to 5 AEs occurred in 90.4% of patients treated with lenvatinib plus pembrolizumab and 82.4% treated with TPC; two patients in the TPC group died due to grade 5 AEs (cardiac failure and toxic cardiomyopathy; both events were considered by the investigator to be treatment related). Adverse events led to dose reductions in 82.7% of patients treated with lenvatinib plus pembrolizumab (dose reductions only for lenvatinib) and 17.6% treated with TPC, interruptions of one or both study drugs in 63.5% and 21.6%, respectively, and discontinuations of one or both study drugs in 36.5% and 7.8%, respectively. The most common AEs were hypertension (78.8%; grade 3–5, 30.8%), hypothyroidism (75.0%; grade 3–5, 0), and proteinuria (63.5%; grade 3–5, 17.3%) with lenvatinib plus pembrolizumab and decreased neutrophil count (66.7%; grade 3–5, 60.8%), nausea (60.8%; grade 3–5, 5.9%), and anemia (47.1%; grade 3–5, 19.6%) with TPC (Table 3). Treatment-related AEs occurred in 98.1% of patients who received lenvatinib plus pembrolizumab and 100% of patients who received TPC (Table S2).

Forty-six patients (88.5%) in the lenvatinib plus pembrolizumab group and three (5.9%) in the TPC group experienced AEs of interest for pembrolizumab regardless of attribution to study treatment by investigators, most of which were mild-to-moderate in severity (Table S3). The most common were hypothyroidism (76.9% and 0, respectively), hyperthyroidism (15.4% and 0, respectively), and infusion reactions (11.5% and 2.0%, respectively). Fifty-one (98.1%) patients in the lenvatinib plus pembrolizumab group and 21 (41.2%) patients in the TPC group experienced clinically significant AEs for lenvatinib regardless of attribution to study treatment by investigators (Table S4). Among 44 (84.6%) patients with lenvatinib dose reductions due to treatment-related intolerable grade 2 AEs or grade 3 AEs, or other reasons, the median time to first dose reduction was 1.4 (range, 0.3–19.6) months (Table S5).

4 | DISCUSSION

Data from the global Study 309/KEYNOTE-775 population evaluating lenvatinib plus pembrolizumab showed statistically significant and clinically meaningful improvements in OS, PFS, and ORR versus TPC after platinum-based chemotherapy in patients with advanced

TABLE 2 Summary of confirmed objective response per RECIST version 1.1 by blinded independent central review

	All-Comer		pMMR	
	Lenvatinib + pembrolizumab $N = 52$	TPC $N = 52$	Lenvatinib + pembrolizumab $N = 44$	TPC $N = 47$
Objective response rate, % (95% CI)	36.5 (23.6–51.0)	26.9 (15.6–41.0)	31.8 (18.6–47.6)	29.8 (17.3–44.9)
Difference vs TPC, % (95% CI)	9.6 (−8.4 to 27.1)		2.0 (−16.9 to 21.0)	
P value	0.147		0.417	
Best overall response, *n* (%)				
Complete response	7 (13.5)	3 (5.8)	5 (11.4)	3 (6.4)
Partial response	12 (23.1)	11 (21.2)	9 (20.5)	11 (23.4)
Stable disease	22 (42.3)	22 (42.3)	20 (45.5)	18 (38.3)
Progressive disease	11 (21.2)	12 (23.1)	10 (22.7)	12 (25.5)
Not evaluable	0	1 (1.9)	0	1 (2.1)
Not assessed	0	3 (5.8)	0	2 (4.3)
Median time to response (range), mo	2.1 (1.7–5.6)	2.0 (1.7–7.4)	2.1 (1.7–3.9)	2.0 (1.7–7.4)
Median duration of response, (range), mo	23.7 (1.6 to 23.7+)	5.2 (2.1+ to 24.2+)	23.7 (1.6 to 23.7+)	5.2 (2.1+ to 24.2+)

Note: "+" indicates no progressive disease reported at the last disease assessment.

Abbreviations: pMMR, mismatch repair-proficient; RECIST, Response Evaluation Criteria in Solid Tumors; TPC, treatment of physician's choice (doxorubicin or paclitaxel).

TABLE 3 Summary of adverse events in all-comer patients (all patients as-treated)

Adverse event	Lenvatinib + pembrolizumab *N* = 52		TPC *N* = 51	
Any	52 (100.0)		51 (100.0)	
Grade 3–5	47 (90.4)		42 (82.4)	
Leading to dose reduction[a]	43 (82.7)		9 (17.6)	
Leading to dose interruption[b]	33 (63.5)		11 (21.6)	
Led to discontinuation of one or both study drugs	19 (36.5)		4 (7.8)	
Pembrolizumab discontinued	8 (15.4)		0	
Lenvatinib discontinued	19 (36.5)		0	
Pembrolizumab and lenvatinib discontinued	6 (11.5)		0	
Led to death[c]	0		2 (3.9)	
Occurring in ≥25% of patients	**Any grade**	**Grade 3–4**	**Any grade**	**Grade 3–4**
Hypertension	41 (78.8)	16 (30.8)	0	0
Hypothyroidism	39 (75.0)	0	0	0
Proteinuria	33 (63.5)	9 (17.3)	4 (7.8)	1 (2.0)
Nausea	25 (48.1)	2 (3.8)	31 (60.8)	3 (5.9)
Platelet count decreased	25 (48.1)	6 (11.5)	7 (13.7)	1 (2.0)
Decreased appetite	24 (46.2)	6 (11.5)	13 (25.5)	0
Palmar-plantar erythrodysesthesia syndrome	24 (46.2)	3 (5.8)	0	0
Diarrhea	23 (44.2)	5 (9.6)	5 (9.8)	0
Anemia	22 (42.3)	7 (13.5)	24 (47.1)	10 (19.6)
Stomatitis	22 (42.3)	2 (3.8)	20 (39.2)	0
Malaise	20 (38.5)	1 (1.9)	17 (33.3)	0
Pyrexia	20 (38.5)	2 (3.8)	6 (11.8)	0
Vomiting	19 (36.5)	0	9 (17.6)	0
Weight decreased	15 (28.8)	7 (13.5)	2 (3.9)	0
Myalgia	14 (26.9)	1 (1.9)	6 (11.8)	0
Alanine aminotransferase increased	13 (25.0)	3 (5.8)	4 (7.8)	0
Arthralgia	13 (25.0)	1 (1.9)	2 (3.9)	0
Headache	13 (25.0)	0	5 (9.8)	0
Neutrophil count decreased	12 (23.1)	6 (11.5)	34 (66.7)	31 (60.8)
White blood cell count decreased	9 (17.3)	4 (7.7)	23 (45.1)	17 (33.3)
Alopecia	6 (11.5)	0	23 (45.1)	0

Note: Data are presented as *n* (%) unless specified otherwise.

Abbreviations: TPC, treatment of physician's choice (doxorubicin or paclitaxel).

[a]For the lenvatinib plus pembrolizumab group, dose reductions for lenvatinib only.

[b]For the lenvatinib plus pembrolizumab group, dose interruption of one or both study drugs (ie, pembrolizumab and/or lenvatinib).

[c]Two patients in the TPC arm had grade 5 treatment-related adverse events: cardiac failure and toxic cardiomyopathy (*n* = 1 each).

endometrial cancer.[8] Overall survival outcomes in our analysis of patients enrolled in Japan (HR in pMMR, 0.74 [95% CI, 0.41–1.34]; HR in all-comers, 0.59 [95% CI, 0.33–1.04]) were consistent with those of the global population, and lenvatinib plus pembrolizumab had a manageable safety profile in patients with advanced endometrial cancer after progression on platinum-based chemotherapy. Notably, the treatment effect for PFS among the Japanese population was reduced (HR in pMMR, 1.04 [95% CI, 0.63–1.73]; HR in all-comers, 0.81 [95% CI, 0.50–1.31]) compared with the global population (HR in pMMR, 0.60 [95% CI, 0.50–0.72]; HR in all-comers, 0.56 [95% CI, 0.47–0.66]).[8] This may have been due, at least in part, to the improved efficacy observed with TPC in Japanese patients (median PFS in pMMR, 5.6 months; median PFS in all-comers, 5.4 months; ORR in pMMR, 29.8%; ORR in all-comers, 26.9%) compared with TPC in the global population (median PFS in pMMR, 3.8 months; median PFS in all-comers, 3.8 months; ORR in pMMR, 15.1%; ORR in all-comers, 14.7%).[8] Additionally, differences in baseline characteristics between the Japanese subset and global population, beyond those included as stratification factors, could have led to the differences observed in Japanese patients. It is important to note that although

the study was not designed or powered to demonstrate statistical superiority in the Japanese subgroup, this analysis shows favorable efficacy and manageable safety of lenvatinib plus pembrolizumab.

Compared with the global population,[8] more patients in the Japanese population had ECOG PS of 0 and low-grade endometrial cancer, and fewer had serous or clear cell carcinoma (considered to be more aggressive histologies[9]), which may have resulted in better baseline prognosis in the Japanese population. More patients in the Japanese population received two prior lines of platinum-based treatment and/or received prior neoadjuvant or adjuvant treatment, and fewer patients received pelvic radiation compared with the global population.[8]

Lenvatinib plus pembrolizumab showed a manageable safety profile in Japanese patients, similar to that in the global study population.[8] The most frequently occurring AEs were hypertension, hypothyroidism, and proteinuria with lenvatinib plus pembrolizumab and decreased neutrophil count, nausea, and anemia with TPC. These results were largely similar to that in Study 111/KEYNOTE-146[7] and the Study 309/KEYNOTE-775 global population.[8] Of note, the proportion of patients with proteinuria, hypothyroidism, and palmar-plantar erythrodysesthesia was higher in the Japanese population compared with the global population.[8] Hypothyroidism and proteinuria were also among the most common treatment-related AEs observed in a phase 1 study of lenvatinib plus pembrolizumab in Japanese patients with advanced solid tumors, although no data on outcomes in patients with endometrial cancer were available.[10] Increased incidences of these AEs have been previously reported in Asian patients receiving VEGF or VEGF receptor inhibitors.[11–15] A number of hypotheses have been proposed to explain the higher incidence of such events among Asian patients receiving VEGF receptor inhibitors, including lower body weight/body surface area and/or genetic differences; evidence supporting these hypotheses has been equivocal.[12,16] Although the incidence of these events was increased among Japanese patients in Study 309/KEYNOTE-775, they did not appear to result in increased rates of discontinuation of ≥1 study drug due to AEs (global population, 33.0% with lenvatinib plus pembrolizumab and 8.0% with TPC[8]; Japan subgroup, 36.5% with lenvatinib plus pembrolizumab and 7.8% with TPC), suggesting that management of these AEs was appropriate. It will be important to ensure clinicians are informed on effective AE management.[17]

In summary, this analysis indicates clinical benefit of lenvatinib plus pembrolizumab in patients enrolled in Japan with advanced endometrial cancer after progression on platinum-based chemotherapy. Together with the global results of Study 309/KEYNOTE-775,[8] the OS advantage demonstrated in the Japanese subgroup supports the use of lenvatinib plus pembrolizumab as a new standard of care for Japanese patients with advanced endometrial cancer.

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DATA AVAILABILITY STATEMENT

Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD) is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The

MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the United States and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

ETHICAL APPROVAL

The authors declare that the research protocol was approved by an Institutional Reviewer Board.

INFORMED CONSENT

All patients provided written informed consent before participating in the study.

ORCID

Kan Yonemori https://orcid.org/0000-0002-7624-7611
Kazuhiro Takehara https://orcid.org/0000-0001-8808-3338
Kosei Hasegawa https://orcid.org/0000-0002-1903-7001

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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