Supplemental Methods

Inclusion and exclusion criteria

In the EC cohort, patients had pathologically confirmed metastatic EC with ≤2 prior lines of systemic therapy. BP was required to be adequately controlled, with or without antihypertensives (defined as ≤150/90 mmHg at screening, with no change in antihypertensive medication within 1 week prior to onset of study treatment). Patients were also required to have adequate renal function (defined as creatinine ≤1.5 × upper limit of normal [ULN] or calculated creatinine clearance ≥40 mL/min per the Cockcroft and Gault formula with creatinine levels >1.5 × ULN); and adequate hepatic function (defined as bilirubin ≤1.5 × ULN and alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase ≤3 × ULN; or in the case of patients with liver metastases ≤5 × ULN). Patients who had >1+ proteinuria on urinalysis underwent 24-hour urine collection for quantitative assessment of proteinuria, and patients with urine protein ≥1 g/24-hour were ineligible. Toxicities that were related to prior treatments were required to have been resolved to grade ≤1.

Study 111/KEYNOTE-146 endpoints

Primary and secondary endpoints were measured by investigator using immune-related (ir)RECIST and modified (m)RECIST criteria. The primary endpoint was ORR at week 24. Secondary endpoints included safety and tolerability, progression-free survival, overall survival, duration of response, disease control rate, and clinical benefit rate. AEs were graded according to CTCAE v4.03, with grades 1-4 indicating increasing severity, and grade 5 indicating death (Supplemental Table 1). Exploratory endpoints included tumor responses by both irRECIST and mRECIST v1.1 as assessed by independent imaging review and antitumor activity according to programmed death-ligand 1 (PD-L1) status.

Adverse reaction criteria

ARs may have occurred while the patient was receiving lenvatinib plus pembrolizumab or either study drug alone. According to the study protocol, dose reductions should only occur following an interruption. Therefore, dose modifications of lenvatinib reported within the manuscript are based on
the final modification of lenvatinib dose per patient (ie, patients who received a dose interruption followed by a dose reduction are reported only as a dose reduction).

Supplemental Results

Dose modifications (because of treatment-emergent adverse events) and exposure

At data cutoff (January 10, 2019), 25.5% of patients with EC that was not MSI-H or dMMR were still undergoing study treatment and 74.5% of patients discontinued treatment (both lenvatinib and pembrolizumab). The most common primary reasons for discontinuation were radiologic disease progression (46.8%), AEs (9.6%), and clinical disease progression (8.5%).

Among patients with EC that was not MSI-H or dMMR, 69.1% had their dose of lenvatinib reduced, and most of these reductions occurred within the first 4 months of treatment (Supplemental Table 2). Among these patients with lenvatinib dose reductions, the mean time to first lenvatinib dose reduction was 2.53 months (standard deviation [SD] 2.55). The TEAEs that most frequently led to dose reduction of lenvatinib were fatigue (19.1%), PPES (12.8%), and hypertension (11.7%). Of patients who received dose reductions, 29.8% received a single dose reduction, 23.4% received two dose reductions, 7.4% received three dose reductions, and 8.5% received four dose reductions. No patient received more than four dose reductions.

Similarly, 71.3% of patients had a dose interruption of lenvatinib (Supplemental Table 2). The mean time to dose interruption was 2.50 months (SD 4.01). The TEAEs that most frequently led to a dose interruption of lenvatinib were hypertension (14.9%), diarrhea (13.8%), and fatigue (10.6%). Furthermore, 48.9% of patients had TEAEs that led to a dose interruption of pembrolizumab. The TEAEs that most frequently led to dose interruption of pembrolizumab were fatigue (7.4%), asthenia (6.4%), decreased appetite (6.4%), and diarrhea (6.4%).

TEAEs leading to discontinuation of both study drugs occurred in 16.0% of patients, TEAEs leading to lenvatinib discontinuation occurred in 22.3% of patients, and TEAEs leading to pembrolizumab discontinuation occurred in 20.2% of patients. TEAEs that led to discontinuation of lenvatinib in more than one patient were pancreatitis (n=2) and muscular weakness (n=2); TEAEs that led to discontinuation of pembrolizumab in more than one patient were adrenal insufficiency (n=2), ischemic colitis (n=2), pancreatitis (n=2), and muscular weakness (n=2). The median duration of lenvatinib treatment was 7.21 months, and the median dose intensity of lenvatinib was 14.34 mg/day. The median
relative dose intensity of lenvatinib was 71.69% of the planned dose. The median duration of pembrolizumab treatment was 6.37 months, and the median number of pembrolizumab dose administrations was 9.5.

Efficacy: Reduction in tumor size and response patterns

Efficacy analyses were conducted in patients with EC that was not MSI-H or dMMR in Study 111/KEYNOTE-146 (n=94). Median tumor shrinkage over time was calculated in patients with baseline tumor assessments (n=88). A median tumor reduction was seen over time, indicating that tumor shrinkage continued to be observed, even if at a slower rate, and in patients with a treatment duration of more than 1 year (Supplemental Fig. 1). Among all patients who had a response (n=36), the dose of lenvatinib prior to the response was 20 mg (n=23), 14 mg (n=9), 10 mg (n=3), or 8 mg (n=1). The dose interruptions, reductions, and discontinuations and response durations among patients who responded can be seen in Supplemental Fig. 2.

Management of selected adverse reactions

Early recognition and intervention, as well as preventative measures where possible, are crucial for optimal management of ARs. Dosing interventions including judicious dose interruptions for lenvatinib and pembrolizumab and dose reductions for lenvatinib in accordance with study protocol guidance were utilized as management strategies for ARs.

For most of the assessed ARs that are attributed to lenvatinib, the management advice from the lenvatinib PI is to withhold lenvatinib for persistent or intolerable grade 2 or grade 3 ARs. On resolution to grade ≤1 or baseline, lenvatinib can be resumed at a lower dose. It is recommended to permanently discontinue lenvatinib for most grade 4 ARs (Lenvima PI). Management advice from the Study 111/KEYNOTE-146 study protocol was similar, with the difference that patients resumed lenvatinib on resolution to tolerable grade 2 or grade ≤1. The ARs assessed in this post hoc analysis that utilized the management strategy outlined in the study protocol are fatigue, nausea and vomiting, diarrhea, decreased appetite and weight loss, PPES, musculoskeletal pain, and stomatitis. Hypertension, hypothyroidism, and proteinuria have more specific management recommendations and are described below in detail.

Guidance for the management of immune-related ARs not included in this analysis (including but not limited to pneumonitis, colitis, hepatitis, endocrinopathies except for hypothyroidism, type 1 diabetes, renal dysfunction, and skin reactions), includes withholding and discontinuation of pembrolizumab; specific management guidance can be found in the pembrolizumab PI (Keytruda PI).
Specific inclusion criteria and recommendations for management of treatment-emergent hypertension from the 111/KEYNOTE-146 clinical study protocol are described below. The prescribing information for lenvatinib should be used for additional guidance. Briefly, patients enrolled were required to have a BP of ≤150/90 mm Hg at time of study entry. Patients with hypertension at baseline were required to be on a stable dose of antihypertensive therapy for at least 1 week before study onset. During the treatment period of the study, patients with systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored on day 15 of each cycle, or more frequently as clinically indicated, until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 3 consecutive months. During the study, antihypertensive agents were recommended as soon as elevated BP (systolic ≥140 mm Hg or diastolic ≥90 mm Hg) was confirmed on two assessments a minimum of 1 hour apart. If patients were already on antihypertensive medications, dose or medication choice was modified. Optimization of medical management for hypertension was recommended prior to lenvatinib interruption or dose reduction. Lenvatinib was withheld if a patient was at imminent risk to develop a hypertensive crisis or had significant risk factors for complications. If elevated BP persisted despite maximal antihypertensive therapy, lenvatinib was to be interrupted and resumed at a lower dose after the patient had been on a stable dose of antihypertensive therapy for ≥48 hours.

The lenvatinib PI also suggests monitoring thyroid function prior to initiating lenvatinib and at least monthly during treatment, and treating according to standard medical practice. Similarly, the pembrolizumab PI recommends monitoring patients for changes in thyroid function at treatment onset and periodically throughout treatment; moreover, it suggests administration of replacement hormones as appropriate. According to the PI, pembrolizumab should be withheld for grade 3-4 events until clinically stable or discontinued depending on severity, and the study protocol for this analysis instructs initiation of thyroid replacement hormones (levothyroxine or liothyronine) for grades 2-4 per standard of care. Pembrolizumab can be continued if hypothyroidism is controlled with thyroid replacement hormones.

Specific recommendations for management of treatment-emergent proteinuria from the 111/KEYNOTE-146 clinical study protocol are included, and the prescribing information for lenvatinib should be used for additional guidance. Proteinuria should be assessed regularly, with grading based on the 24-hour urinary protein result. A 24-hour urine collection (within 72 hours) to verify the grade of proteinuria for protein quantitation was required if: the initial occurrence of proteinuria on urine dipstick while on study drug was ≥2+; a subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level was observed; or there had been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result was 2+, 3+, or 4+. Urine dipstick testing for patients with proteinuria ≥2+ should have been performed on day 15 (or more frequently as clinically indicated) until the results were 1+ or negative for 3 consecutive months. Grading of proteinuria was performed
according to CTCAE v4.03 (Supplemental Table 1) based on the 24-hour urine collection for total protein result, if a 24-hour urine test was performed at that time point. For patients with lenvatinib-related toxicity, the dose reduction and/or interruption instructions described above for general toxicity management should be followed. The lenvatinib PI recommends withholding lenvatinib in the case of 2+ grams of proteinuria per 24 hours and resuming at a reduced dose, and discontinuation of lenvatinib in the case of nephrotic syndrome.

**Supplemental References**

Lenvima (lenvatinib) [prescribing information]. Woodcliff Lake, NJ, USA: Eisai Inc., 2020.

Keytruda (pembrolizumab) [package insert]. Whitehouse Station, NJ, USA: Merck Sharp & Dohme Corp., 2020.