Secondary	
• Objective: To compare the objective response rate (ORR) of participants treated with lenvatinib in combination with pembrolizumab versus TPC by BICR. Hypothesis (H3): The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by ORR in pMMR participants. Hypothesis (H6): The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by ORR in all-comer participants.	• ORR, defined as the proportion of participants who have best overall response of either complete response (CR) or partial response (PR), as determined by BICR per RECIST 1.1.
• Objective: To evaluate the impact of treatment on Health-Related Quality of Life (HRQoL) as assessed by using the global score of the European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30 for participants treated with lenvatinib in combination with pembrolizumab versus TPC in pMMR and in all-comer participants.	• HRQoL will be assessed using the global score of the EORTC QLQ-C30.
• Objective: To assess safety and tolerability of treatment with lenvatinib in combination with pembrolizumab versus TPC in pMMR participants and in all-comer participants.	• Incidence of treatment-emergent adverse events (TEAEs), serious AEs (SAEs), and immune-related AEs. • Proportion of participants discontinuing study treatment due to TEAEs. • Time to treatment failure due to toxicity, defined as the time from the date of randomization to the date that a participant discontinues study treatment due to TEAEs.

Study Period	**Screening[a]**	**Treatment Period Arm A: 21-Day Cycles Arm B: 21-Day or 28-Day Cycles**									**EOT**	**Post Treatment Visits**			**Notes**
Treatment Cycle		**Cycle 1**			**Cycle 2**			**Cycle 3 - last**							
Cycle Day		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**		**Safety FU[b]**	**Efficacy FU Visits**	**Survival FU**	
Scheduling Window (Days):	**–28 to –1**		**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W[c] (± 7 days)**	**Q12W (± 7 days)**	
Demographics	X														
Medical/surgical history	X														Significant medical history to be captured for last 10 years. All medical history related to any cancer other than EC should be collected, regardless of when it occurred.
FIGO staging	X														At initial diagnosis; see protocol Appendix 7
Prior/ concomitant medication review[c]	X	X	X	X	X	X	X	X	X	X	X	X	X		Concomitant medications will be recorded for 30 days after last dose (or for up to 120 days after last dose for SAEs), including any anticancer therapies taken for any cancer other than EC.
Randomization and study treatment assignment via IRT		X													Participants may be randomized up to 3 days prior to C1D1. All screening procedures, if performed on the date of randomization, must be performed prior to randomization.
Subsequent anti-neoplastic treatment												X	X	X	All anticancer therapy will be recorded until time of death or termination of survival follow-up. If a clinic visit is not feasible, follow-up information may be obtained via telephone or e-mail.

Study Period	**Second Course Phase (Retreatment) 21-Day Cycles**								**EOT**	**Post Treatment Visits**			**Notes**
Treatment Cycle	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8-17**					
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**		**Safety FU**	**Efficacy FU Visit**	**Survival FU**	• **If EOT visit occurs ≥30 days from last dose of study treatment, a safety follow-up visit is not required. In this situation, all procedures required at both the EOT visit and the safety follow-up visit should be performed**
Scheduling Window (Days):		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**30 Days After Last Dose (+ 7 days)**	**Q12W (±7 days)**	**Q12W (± 7 days)**	
Efficacy Procedures													
Tumor assessment (CT/MRI)	<---------->								X		X		All imaging visits have a scheduling window of ±7 days. Imaging to be performed within 28 days prior to restarting treatment in Second Course and then Q12W, or sooner if clinically indicated. Imaging at EOT is not required if the previous tumor imaging assessment was within 4 weeks prior to the EOT visit.
Bone scan	<---------->								X				Only for participants with a history of bone metastases or who are clinically symptomatic. All imaging visits have a scheduling window of ±7 days. A bone scan is required prior to restarting treatment in the Second Course Phase, only if the previous imaging assessment was not performed within 6 weeks of restarting treatment, and then Q24W, or as clinically indicated. Imaging at EOT is not required if the previous tumor imaging assessment was within 4 weeks prior to the EOT visit.

Study Period	**Eligibility[a]**	**Crossover Phase (21-Day Cycles)**									**EOT**	**Post-Crossover Phase Visits**			**Notes**
Treatment Cycle		**Cycle 1**			**Cycle 2**			**Cycle 3 – Last**							
Cycle Day		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**		**Safety FU[b]**	**Efficacy FU Visits**	**Survival FU**	
Scheduling Window (Days):	**–28 to –1**		**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**30 Days After Last Dose (+ 7 days)**	**Q12W[d] (± 7 days)**	**Q12W (± 7 days)**	
Administration of Study Treatment															
Lenvatinib plus pembrolizumab		X			X			X							Lenvatinib 20 mg QD plus pembrolizumab 200 mg Q3W; 21-day cycle.
Efficacy Procedures															
Tumor assessment – chest, abdomen and pelvis (CT/MRI)[d]	X	⟷									X		X		All imaging visits have a scheduling window of ±7 days. Imaging to be performed Q12W from first dose of crossover at C1D1 or sooner if clinically indicated until confirmation of disease progression per RECIST 1.1. Imaging at EOT is not required if the previous tumor imaging assessment was within 4 weeks prior to the EOT visit.

Objective/Hypothesis	Endpoint
Secondary	
• Objective: To compare the objective response rate (ORR) of participants treated with lenvatinib in combination with pembrolizumab versus TPC by BICR Hypothesis (H3): The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by ORR in pMMR participants. Hypothesis (H6): The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by ORR in all-comer participants.	• ORR, defined as the proportion of participants who have best overall response of either complete response (CR) or partial response (PR), as determined by BICR per RECIST 1.1.
• Objective: To evaluate the impact of treatment on Health-Related Quality of Life (HRQoL) as assessed by using the global score of the European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30 for participants treated with lenvatinib in combination with pembrolizumab versus TPC in pMMR participants and in all-comer participants.	• HRQoL will be assessed using the global score of the EORTC QLQ-C30.
• Objective: To assess safety and tolerability of treatment with lenvatinib in combination with pembrolizumab versus TPC in pMMR participants and in all-comer participants.	• Incidence of treatment-emergent adverse events (TEAEs), serious AEs (SAEs), and immune-related AEs. • Proportion of participants discontinuing study treatment due to TEAEs. • Time to treatment failure due to toxicity, defined as the time from the date of randomization to the date that a participant discontinues study treatment due to TEAEs.
• Objective: To characterize the population pharmacokinetics (PK) of lenvatinib when co-administered with pembrolizumab in pMMR participants and in all-comer participants.	• Plasma concentration of lenvatinib versus time.

the following 2 treatment arms in a 1:1 ratio, with approximately 390 participants in each arm:

- Arm A: lenvatinib 20 mg (orally, QD) plus pembrolizumab 200 mg (IV Q3W)
- Arm B: TPC consisting of either doxorubicin 60 mg/m^2 (by IV bolus injection, 1-hour infusion, or per institutional guidelines) Q3W, or paclitaxel 80 mg/m^2 (by 1-hour IV infusion or per institutional guidelines) given weekly, 3 weeks on/1 week off

The study will have been considered to have completed enrollment when 660 pMMR participants have enrolled. Enrollment of dMMR participants will be capped at 120.

Prior to randomization, investigators must select and record the TPC option in the event the participant will be assigned to that arm. Randomization will follow a predefined randomization scheme based on the following stratification factors: MMR status (pMMR or dMMR), ECOG performance status (0 or 1), geographic region (Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel or Region 2: rest of the world), and prior history of pelvic radiation (yes or no). First, participants will be stratified according to MMR status. Then, only within the pMMR stratum, participants will be further stratified according to ECOG performance status, geographic region, and prior history of pelvic radiation. A total of 9 strata will be utilized for the study.

The end of the study will be the date of data cutoff for the final OS analysis (ie, 526 deaths in pMMR participants) or the time of last participant/last treatment, whichever occurs later.

4.1.1 Screening Period

Screening will occur between Day -28 and Day -1. The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility according to the inclusion and exclusion criteria listed in Section 5.1 and Section 5.2, respectively.

Informed consent will be obtained after the study has been fully explained to each participant and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 8.1.1.

Eligible participants must have measurable disease according to RECIST 1.1 [Eisenhauer, E. A., et al 2009] confirmed by BICR prior to randomization. Available historical tumor or fresh tumor biopsy specimen must be submitted for all participants prior to randomization for determination of MMR status by a designated central laboratory.

Laboratory tests should be performed within 7 days of the first dose of study treatment. A pregnancy test (for women of childbearing potential [WOCBP]) should be performed within 72 hours of the first dose of study treatment. Repeated laboratory evaluation to establish eligibility is not allowed unless discussed and agreed upon with MSD.

Participants who complete the Screening Period and meet the criteria for inclusion/exclusion (Sections 5.1 and 5.2) will begin the Treatment Period. The appropriate case report form (CRF) page must be completed to indicate whether the participant is eligible to participate in the study and to provide reasons for screen failure, if applicable. If the MMR result is not available within 28 days from when the original consent was obtained, an extension may be granted after consultation with MSD as long as all other screening procedures are performed within the correct timeframe.

4.2.2 Rationale for Endpoints

4.2.2.1 Efficacy Endpoints

This study will use PFS based on RECIST 1.1 criteria as assessed by BICR and OS as the primary endpoints. Progression-free survival is an acceptable measure of clinical benefit for a late stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The use of BICR and RECIST 1.1 to assess PFS is typically considered acceptable by regulatory authorities. Images will be read by a CIV blinded to treatment assignment to minimize bias in the response assessments. In addition, the final determination of radiologic progression will be based on the central assessment of progression, rather than a local site investigator/radiology assessment. Real time determination of radiologic progression as determined by central review will be communicated to the site.

Overall survival has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies.

4.2.2.1.1 RECIST 1.1

RECIST 1.1 will be used by the BICR when assessing images for efficacy measures and by the local site when determining eligibility (Section 8.2.1.5). Although traditional RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented a modification to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ.

4.2.2.1.2 CCI

CCI

CCI [redacted]

4.2.2.2 Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/serious AEs (SAEs), and changes in vital signs and laboratory values. Adverse events will be assessed as defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03.

4.2.2.3 Rationale for Patient Reported Outcomes

Symptomatic improvement is considered a clinical benefit and accepted by health authorities. As part of the analyses for this study, participants will provide information regarding their health-related QoL (HRQoL) via the following assessment tools: European Organisation for the Research and Treatment of Cancer (EORTC) QLQ-C30, CCI [redacted] and the CCI [redacted] questionnaires. These measures are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.2.3.1 EORTC QLQ-30

The EORTC QLQ-C30 is the most widely used cancer-specific health-related quality of life (QoL) instrument, which contains 30 items and measures 5 functional dimensions (physical, role, emotional, cognitive, and social), 3 symptom items (fatigue, nausea/vomiting, and pain), 6 single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health and QoL scale [Aaronson, N. K., et al 1993]. The EORTC QLQ-C30 is a psychometrically and clinically validated instrument appropriate for assessing QoL in oncology studies [Aaronson, N. K., et al 1993].

4.2.2.3.2 CCI [redacted]

CCI [redacted]

4.2.2.3.3 CCI [redacted]

CCI [redacted]

CCI [redacted]

4.2.2.4 Pharmacodynamic Endpoints

No pharmacodynamic endpoints are planned for this study.

4.2.2.5 CCI [redacted]

CCI [redacted]

CCI

[redacted]

4.2.3 Rationale for the Use of Comparator

The TPC options of doxorubicin or paclitaxel will be used as a comparator to reflect standard clinical practice.

randomly in a 1:1 ratio to either Arm A (lenvatinib + pembrolizumab) or Arm B (TPC), respectively.

6.3.1.1 Stratification

Treatment allocation/randomization will be stratified according to the following factors:

1. MMR status (pMMR or dMMR)
2. ECOG performance status (0 or 1)
3. Geographic region (Region 1 [Europe, USA, Canada, Australia, New Zealand, and Israel] or Region 2 [rest of the world])
4. Prior history of pelvic radiation (yes or no)

First, participants will be stratified according to MMR status. Then, only within the pMMR stratum, participants will be further stratified according to ECOG performance status, geographic region, and prior history of pelvic radiation. A total of 9 strata will be utilized for the study.

6.3.2 Blinding

This study is an open-label study; therefore, the Sponsor, MSD, investigator and participant will know the treatment administered.

6.4 Treatment Compliance

Interruptions from the protocol specified treatment plan for >28 days (lenvatinib and TPC) or for >6 weeks (pembrolizumab) require consultation between the investigator and MSD and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the treatment period. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study treatment may be required. The investigator should discuss any questions regarding this with the MSD Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, MSD, the Sponsor, and the participant.

Any medication (including over-the-counter medications) or therapy administered to the participant during the study (starting at the date of informed consent) will be recorded on the appropriate CRF. The investigator will record the AE for which the concomitant medication/therapy was administered on the appropriate CRF. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the appropriate CRF.

All prior medications (including over-the-counter medications) administered 30 days before the first dose of study drug and any concomitant therapy administered to the participant during the course of the study (starting at the date of informed consent) until 30 days after the

participants should be instructed to report such symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in Table 3 should be followed. Appropriate supportive care should be provided together with close monitoring. If a participant experiences life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism, lenvatinib must be discontinued.

Arterial thromboembolic events (eg, new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, and cerebrovascular accident) of any grade require study treatment discontinuation.

6.6.1.6 Management of Posterior Reversible Encephalopathy Syndrome/Reversible Encephalopathy Syndrome/Reversible Posterior Leukoencephalopathy Syndrome

Posterior Reversible Encephalopathy Syndrome/Reversible Encephalopathy Syndrome/ Reversible Posterior Leukoencephalopathy Syndrome (PRES/RPLS) is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. MRI is necessary to confirm the diagnosis of PRES/RPLS. Appropriate measures should be taken to control BP. In participants with signs or symptoms of PRES/RPLS, instructions in Table 3 should be followed.

6.6.1.7 Management of Hypocalcemia

Serum calcium should be monitored per the SoA (Section 1.3.1 and Section 1.3.2). Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v4.03, using the following formula:

$$\text{Corrected calcium} = ([4 - \text{serum albumin in g/dL}] \times 0.8 + \text{serum calcium})$$

The formula is not applicable when serum albumin concentration is normal (>4 g/dL); in such situations, the total (uncorrected) serum calcium should be used instead.

Hypocalcemia should be treated per institutional guidelines (eg, using appropriate calcium, magnesium, and vitamin D supplementation) until resolution.

6.6.1.8 Management of Hemorrhage

Instructions in Table 3 should be followed for the management of hemorrhage. Either resume at a reduced dose or discontinue lenvatinib depending on the severity and persistence of hemorrhage.

6.6.1.9 Management of Gastrointestinal Perforation or Fistula Formation

Lenvatinib should be discontinued in any participants who develop gastrointestinal perforation of any grade or any Grade 4 gastrointestinal or non-gastrointestinal fistula.

A copy of the signed and dated consent form should be given to the participant before participation in the study.

The initial ICF, any subsequent revised written ICF and any written information provided to the participant must receive the Institutional Review Board/Independent Ethics Committee's (IRB/IEC's) approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations and MSD requirements.

If the investigator recommends continuation of study intervention beyond disease progression, the participant or her legally acceptable representative will be asked to sign consent.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the study and Crossover Phase, if applicable.

8.1.3 Participant Identification Card

All participants will be given a Participant Identification Card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the participant with a Participant Identification Card immediately after the participant provides written informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Participant Identification Card.

The participant identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study treatment in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically significant. All medical history related to any cancer other than EC should be collected, regardless of when it occurred.

Comprehensive details regarding the participant's EC history will be recorded separately and not listed as medical history. These details include but are not limited to FIGO stage at initial diagnosis, histopathology, location(s) of tumor burden, and all prior treatment (including prior radiation, prior chemotherapy, and prior surgery).

8.2.1.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to the date of randomization. The site study team must submit screening images to the CIV to confirm the participant has measurable disease per RECIST 1.1.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if it is of diagnostic quality and performed within 28 days prior to the date of randomization and can be assessed by the CIV.

If brain imaging is performed to document the stability of existing metastases, MRI should be used if possible. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.

Tumor imaging at baseline includes the following:

- CT or MRI (preferred) of the abdomen and pelvis
- CT of the chest
- Bone scan for participants with a history of bone metastases or who are clinically symptomatic
- Brain scan for participants with a history of protocol-eligible treated brain metastases or who are clinically symptomatic

8.2.1.2 Tumor Imaging During the Study

The first on study imaging assessment should be performed at 8 weeks (56 days ±7 days) from the date of randomization. Subsequent tumor imaging should be performed every 8 weeks (56 days ±7 days) or more frequently if clinically indicated. Following the primary analysis for the study, tumor imaging should be performed Q12W (84 days ±7 days) or more frequently if required by local standard of care and bone and brain scans should be performed per local standard of care. Imaging timing should follow calendar days from randomization and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the Investigator and verified by the CIV CCI the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first. All supplemental imaging must be submitted to the CIV.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point. Note: Response does not typically need to be verified in real time by the CIV.

CCI

CCI [redacted]

8.2.3 Crossover Phase Assessments and Procedures

Crossover participants can initiate treatment with lenvatinib 20 mg QD plus pembrolizumab 200 mg Q3W once investigators confirm that participant meets the required eligibility criteria. All inclusion/exclusion criteria should be met to participate in the crossover phase, except for exclusions #20, #21, #24 and #28 (Sections 5.1 and 5.2). The participant will then start the Crossover Phase as outlined in the Crossover SoA in Section 1.3.3. Participants must have baseline imaging scans performed within 30 days prior to the first dose of lenvatinib plus pembrolizumab in the Crossover Phase.

On study imaging will be performed every 12 weeks (84 ±7 days) from the first dose of Crossover study treatment or more frequently, if clinically indicated. Local reading of imaging (investigator assessment with site radiology reading) will be used for participant management. During Crossover Phase, imaging scans no longer need to be sent to the CIV.

Participants may continue on lenvatinib plus pembrolizumab until investigator-assessed progressive disease as assessed by RECIST 1.1 (as described in Section 8.2.1 and Table 6) and only when clinically appropriate, CCI [redacted] or up to two years (35 cycles) from starting crossover treatment on C1D1 with lenvatinib 20 mg plus pembrolizumab 200 mg Q3W, whichever comes first. In participants who discontinue treatment in the Crossover Phase without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 12 weeks (±7 days) until (1) the start of post-crossover new anticancer treatment, (2) disease progression, (3) death, or (4) the end of the study, whichever occurs first.

Participants who discontinue study treatment in the Crossover Phase will follow the post-crossover phase procedures as outlined in Sections 1.3.3 and 8.12.3.

As described in Section 7.1.1, participants who attain a confirmed CR per RECIST 1.1 will have the option to hold lenvatinib plus pembrolizumab while continuing in the study. Please note the following exception: crossover participants will not be eligible for Second Course Phase as outlined in Section 6.6.5.

8.3 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all NCI CTCAE v4.03 grades (for both increasing and decreasing severity), and SAEs; regular laboratory evaluation for hematology, blood chemistry, and urine values; periodic measurement of vital signs, ECGs and MUGA or echocardiogram; and the performance of physical examinations as detailed in Section 1.3.

Progression of EC and signs and symptoms clearly related to the progression of EC should not be captured as an AE. Disease progression is a study endpoint and should be captured in the CRF as per the guidelines for reporting disease progression.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

Physical examinations (comprehensive or symptom-directed) will be performed as specified in the SoA (Section 1.3.1, Section 1.3.2, and Section 1.3.3). A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination.

Documentation of the physical examination will be included in the source documentation at the investigational site. Significant findings prior to participant informed consent will be recorded on the appropriate CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the appropriate CRF.

8.3.2 Vital Signs

Vital sign measurements (ie, systolic and diastolic BP [mm Hg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in the SoA (Section 1.3.1 and Section 1.3.2) by a validated method.

- Blood pressure and heart rate will be measured after the participant has been resting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.
- Only 1 BP measurement is needed for participants with systolic BP <140 mm Hg and diastolic BR <90 mm Hg. If the participant's first BP measurement of the current assessment is elevated (ie, systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), the BP measurement should be repeated at least 5 minutes later. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.
- Under exceptional circumstances, participants will have the option of having BP measured between visits obtained locally by a health care professional. A diary will be provided as a tool to aid the participant in collecting BP evaluations between study visits.

8.3.3 Electrocardiograms

Electrocardiograms will be obtained as designated in the SoA (Section 1.3.1, Section 1.3.2, and Section 1.3.3). Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Participants must be in the

8.3.5.1 Hematology and Clinical Chemistry

Hematology and clinical chemistry results must be reviewed prior to administration of study therapy. Electrolytes such as potassium, calcium, and magnesium should be monitored and abnormalities, when considered clinically significant, should be corrected in all participants before starting treatment.

8.3.5.2 Urine Dipstick

Urine dipstick testing is required at the time points specified in the SoA. Additionally, urine dipstick testing is required on Day 15 of Cycles 1 and 2.

Urine dipstick testing for participants with proteinuria ≥2+ should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles. Urine dipstick testing should be performed preferably at the investigational site (but may be performed locally by the primary care physician or a local laboratory if the participant does not have to come for a visit to the site). If a new event of proteinuria ≥2+ occurs, the participant must resume the Day 15 urine dipstick testing for evaluation of proteinuria until results are 1+ or negative for 2 consecutive treatment cycles. For participants with proteinuria ≥2+, see subsection for management of proteinuria section.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Progression of the cancer under study is not considered an AE as described in Section 8.4.5 and Appendix 3.

AE, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AE, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of treatment allocation/randomization through 30 days following cessation of study treatment must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to MSD if the event is considered to be drug-related.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify MSD.

All initial and follow-up AEs, SAEs and other reportable safety events will be recorded and reported to MSD or designee within the time frames as indicated in Table 7.

8.4.6 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to MSD.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.7 Events of Clinical Interest (ECIs)

Selected nonserious and serious adverse events are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. an overdose of study treatment, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow-up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

8.5 Treatment of Overdose

For the purposes of this study, an overdose will be defined as any dose exceeding the prescribed dose for:

- Pembrolizumab: ≥5 times the prescribed dose specified in the protocol.
- Lenvatinib: any dose above the prescribed dose specified in the protocol if associated with an AE.
- Chemotherapy: any dose ≥20% over the prescribed dose specified in the protocol.

No specific information is available on the treatment of overdose of pembrolizumab or lenvatinib. There is no specific antidote for an overdose of lenvatinib. Due to its high degree of plasma protein binding, lenvatinib is not expected to be dialyzable. Adverse reactions in patients receiving single doses of lenvatinib as high as 40 mg were similar to those in clinical studies at the recommended dose for differentiated thyroid cancer, RCC, and HCC.

All reports of pembrolizumab overdose with and without an AE and all reports of lenvatinib overdose with an AE must be reported as specified in Table 7.

Reports of pembrolizumab overdose without any associated clinical symptoms or abnormal laboratory results should be reported using the terminology “accidental or intentional overdose without adverse effect”. The investigator should consult with the Medical Monitor prior to resuming treatment.

8.6 Pharmacokinetics

Blood samples will be collected as specified in the SoA (Section 1.3.1 and Section 1.3.2). Study sites must have appropriately trained staff and adequate equipment for procuring and processing specimens. Instructions for the collection, handling, and shipping procedures of PK samples will be provided in the laboratory manual.

Blood samples will be collected from all participants in Arm A. Plasma concentrations of lenvatinib will be measured. Lenvatinib will be analyzed using a population PK approach.

Lenvatinib will be quantified by use of validated High Performance Liquid Chromatography-tandem mass spectroscopy method.

8.7 Pharmacodynamics

Data from Arm A of the study will be used to explore the relationship between exposure to lenvatinib and safety events related to lenvatinib.

8.8 Mismatch Repair Status

Archived tumor tissue from the most recent surgery/biopsy or from a fresh biopsy (if there is no archival tumor tissue available), will be collected from all enrolled participants for determination of MMR status by central assessment prior to randomization. When available, a tissue sample collected after the latest systemic treatment is preferred.

8.9 CCI

CCI

8.9.1 CCI

CCI

The first survival follow-up assessment should be scheduled as described below:

- For participants who discontinue study treatment and who will not enter the Efficacy Follow-up Phase, the first survival follow-up contact will be scheduled 12 weeks after the discontinuation visit and/or safety follow-up visit (whichever is last).
- For participants who completed assessments in the Efficacy Follow-up Phase, the first survival follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.
- For participants who are in the Crossover phase, the first survival follow-up contact will be scheduled 12 weeks after the investigator-assessed disease progression by RECIST 1.1.
- Participants who are in Survival Follow-up may be eligible for the Crossover Phase if they have an investigator-determined PD (by RECIST 1.1) and meet all eligibility criteria, except exclusions #20, #21, #24 and #28 (Section 8.12.2.1), but have not withdrawn consent (from either study treatment or Efficacy Follow-up), or started a new anticancer therapy.

8.12.4 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an external DMC review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status.

9. Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analysis, will be documented in a supplemental statistical analysis plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Separate analysis plans will be provided for PK, biomarker, and PRO analyses. Post hoc exploratory analyses will be clearly identified in the CSR.

- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI

9.5 Analysis Populations

9.5.1 Efficacy Analysis Population

The Intention to Treat (ITT) population will serve as the population for the primary efficacy analyses. All randomized participants will be included in this population. Participants will be analyzed in the treatment group to which they are randomized.

9.5.2 Safety Analysis Population

The All Participants as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who received at least 1 dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received. For most participants, this will be the treatment group to which they are randomized. Participants who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received. Any participant who receives the incorrect study treatment for 1 cycle, but receives the correct treatment for all other cycles, will be analyzed according to the correct treatment group and a narrative will be provided for any events that occur during the cycle for which the participant is incorrectly dosed.

At least 1 laboratory or vital sign measurement obtained subsequent to at least 1 dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Table 12 Highly Effective Contraception Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen-containing) hormonal contraception [b, c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b, c] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen-only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
Abbreviation: WOCBP = women of childbearing potential. Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 120 days (for participants treated with lenvatinib plus pembrolizumab) or for at least 180 days (for participants treated with TPC) after the last dose of study treatment. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Events NOT meeting the AE definition
● Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. ● Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). ● Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. ● Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened. ● Refer to Section 8.4.5 for protocol specific exceptions

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening ● The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization ● Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of study treatment and is documented in the patient's medical history.
d. Results in persistent or significant disability/incapacity ● The term disability means a substantial disruption of a person's ability to conduct normal life functions. ● This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Any AE which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

Assessment of causality

- Did the study treatment cause the AE?
  - The determination of the likelihood that study treatment caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information
  - **The following components are to be used to assess the relationship between study treatment and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:
    - **Exposure:** Is there evidence that the participant was actually exposed to study treatment such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

10.4 Appendix 4: Clinical Laboratory Tests

- The tests detailed in Table 13 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Abbreviation	Term
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme-linked immunosorbent assay
EOC	Executive Oversight Committee
EORTC	European Organisation for the Research and Treatment of Cancer
EuroQoL	European Quality of Life
FAS	Full Analysis Set
FDA	Food and Drug Administration
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
FIGO	International Federation of Gynecology and Obstetrics
GCP	Good Clinical Practice
HCC	Hepatocellular carcinoma
HIV	Human immunodeficiency virus
HRQoL	Health-Related Quality of Life
HUVEC	Human umbilical vein endothelial cell
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
CCI [redacted]	
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
INR	International normalized ratio
CCI [redacted]	
IRB	Institutional Review Board
CCI [redacted]	
IRR	Independent radiologic review
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
IRT	Interactive response technology
ITT	Intention-to-treat

6.6.1.1 Management of Hypertension

Hypertension is a recognized side effect of treatment with drugs inhibiting VEGF signaling. Investigators should therefore ensure that participants enrolled to receive treatment with lenvatinib have BP of ≤150/90 mm Hg at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before C1D1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Regular assessment of BP should be as detailed in the SoA (Section 1.3.1 and Section 1.3.2). Hypertension will be graded using NCI CTCAE v4.03, based on BP measurements only (and not on the number of antihypertensive medications).

If the participant's first BP measurement of the current assessment is elevated (ie, systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), the BP measurement should be repeated at least 5 minutes later. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg) is confirmed on 2 assessments at least 30 minutes apart. The choice of antihypertensive treatment should be individualized to the participant's clinical circumstances and follow standard medical practice. For previously normotensive participants, appropriate antihypertensive therapy should be started when systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg is first observed on 2 assessments at least 30 minutes apart. For those participants already on antihypertensive medication, treatment modification may be necessary if hypertension persists.

Lenvatinib should be withheld in any instance where a participant is at imminent risk to develop a hypertensive crisis or has uncontrolled hypertension with significant risk factors for severe complications (eg, BP ≥160/100 mm Hg, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant co-morbidities). Once the participant has been on the same antihypertensive medications for at least 48 hours and the BP is controlled, lenvatinib should be resumed as described below.

Participants who have had systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored on Day 15 (or more frequently as clinically indicated) until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles. If a repeat event of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg occurs, the participant must resume the Day 15 evaluation until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles. A diary will be provided to the participant to capture the blood pressure evaluations between study visits.

The following guidelines should be followed for the management of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg confirmed on 2 BP assessments at least 30 minutes apart:

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST / ALT Elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [a]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [a]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or Permanently discontinue [a]		

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AE and/or SAE and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AE, SAE, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), Cancer and Overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

- Prompt notification (within 24 hours) by the investigator to MSD of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The Sponsor and MSD have a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. All AEs will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, per ICH Topic E6 (R2) Guidelines for GCP.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and MSD policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from MSD will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Efficacy endpoints as outlined in this section will not be reported to sponsor/designee as described in Section 8.4.1.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The sponsor/designee will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the participants in the study.

10.5 Appendix 5: CCI [redacted]

CCI [redacted]

• Objective: To characterize the population pharmacokinetics (PK) of lenvatinib when co-administered with pembrolizumab in pMMR participants and in all-comer participants.	• Plasma concentration of lenvatinib versus time.
• Objective: To assess the relationship between exposure to lenvatinib and safety events related to lenvatinib in pMMR participants and in all-comer participants.	• Clearance and area under the concentration-time curve (AUC) for lenvatinib.

Overall Design:

Study Phase	Phase 3
Clinical Indication	Treatment of advanced endometrial cancer
Population	Participants with advanced endometrial cancer who have been treated with at least one prior platinum-based chemotherapy regimen.
Study Type	Interventional
Type of Design	Multicenter, randomized, parallel
Type of Control	Active control without placebo
Study Blinding	Open-label
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 43 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 780 participants (660 mismatch repair [MMR] proficient participants and up to 120 MMR deficient participants) will be randomized to 1 of 2 treatment arms.

Study Period	**Screening[a]**	**Treatment Period Arm A: 21-Day Cycles Arm B: 21-Day or 28-Day Cycles**									**EOT**	**Post Treatment Visits**			**Notes**
Treatment Cycle		**Cycle 1**			**Cycle 2**			**Cycle 3 - last**							
Cycle Day		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**		**Safety FU[b]**	**Efficacy FU Visits**	**Survival FU**	
Scheduling Window (Days):	**–28 to –1**		**±1**	**±1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W[c] (± 7 days)**	**Q12W (± 7 days)**	
Date of progression on subsequent anti-neoplastic treatment												X	X	X	Participants will be followed for CCI (unless this information is not allowed to be provided due to confidentiality).
Phone contact visit			X												Telephone contact or visit on C1D8 will assess participants for development of early toxicity. An unscheduled visit can occur prior to C1D15 if deemed necessary by the investigator.
Survival status		<---------->													Participants will be followed for survival (unless this information is not allowed to be provided due to confidentiality).
Administration of Study Treatment															
Lenvatinib plus pembrolizumab		X			X			X							Lenvatinib 20 mg QD plus pembrolizumab 200 mg Q3W; 21-day cycle.
Doxorubicin		X			X			X							60 mg/m^2 Q3W; 21-day cycle.
Paclitaxel		X	X	X	X	X	X	X	X	X					80 mg/m^2 QW; 3 weeks on, 1 week off of each 28-day cycle.

Study Period	**Second Course Phase (Retreatment) 21-Day Cycles**								**EOT**	**Post Treatment Visits**			**Notes**
Treatment Cycle	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8-17**					
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**		**Safety FU**	**Efficacy FU Visit**	**Survival FU**	• **If EOT visit occurs ≥30 days from last dose of study treatment, a safety follow-up visit is not required. In this situation, all procedures required at both the EOT visit and the safety follow-up visit should be performed**
Scheduling Window (Days):		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At DC**	**30 Days After Last Dose (+ 7 days)**	**Q12W (±7 days)**	**Q12W (± 7 days)**	
Brain scan	<----------	----------	----------	----------	----------	----------	----------	---------->	X				All imaging visits have a scheduling window of ±7 days. Only for participants with a history of protocol-eligible treated brain metastases or who are clinically symptomatic, a brain scan will be required within 28 days of restarting treatment in Second Course and then at all tumor assessment time points (eg, Q8W or as clinically indicated). Imaging at EOT is not required if the previous tumor imaging assessment was within 4 weeks prior to the EOT visit.
Safety Procedures													• **Clinical laboratory assessments may be conducted anytime within 72 hours prior to the scheduled visit, unless otherwise specified.** • **Procedures/assessments should be performed prior to administration of study treatment.**
AE monitoring	X	X	X	X	X	X	X	X	X	X	X		AEs: monitored up to 30 days after last dose. SAEs and pregnancy: monitored up to 120 days after last dose, or 30 days after last dose if participant starts a new anticancer therapy, whichever is sooner.
Vital signs (resting BP, HR, RR, and temp) and weight	X	X	X	X	X	X	X	X	X	X			

Study Period	Eligibility[a]	Crossover Phase (21-Day Cycles)									EOT	Post-Crossover Phase Visits			Notes
Treatment Cycle		Cycle 1			Cycle 2			Cycle 3 – Last							
Cycle Day		1	8	15	1	8	15	1	8	15		Safety FU[b]	Efficacy FU Visits	Survival FU	
Scheduling Window (Days):	–28 to –1		±1	±1	±3	±3	±3	±3	±3	±3	At DC	30 Days After Last Dose (+ 7 days)	Q12W[d] (± 7 days)	Q12W (± 7 days)	
Bone scan[d]	X	<---------->									X		X		Only for participants with a history of bone metastases or who are clinically symptomatic. All imaging visits have a scheduling window of ±7 days. A bone scan is required prior to starting treatment in the Crossover Phase, only if the previous imaging assessment was not performed within 6 weeks of initial treatment, and then Q24W, or as clinically indicated. Imaging at EOT is not required if the previous tumor imaging assessment was within 4 weeks prior to the EOT visit.
Brain scan[d]	X	<---------->									X		X		All imaging visits have a scheduling window of ±7 days. Only for participants with a history of protocol-eligible treated brain metastases or who are clinically symptomatic, a brain scan will be required within 28 days from starting treatment in Crossover Phase, and at all tumor assessment time points (eg, Q12W or as clinically indicated) Imaging at EOT is not required if the previous tumor imaging assessment was within 4 weeks prior to the EOT visit.

Objective/Hypothesis	Endpoint
• Objective: To assess the relationship between exposure to lenvatinib and safety events related to lenvatinib in pMMR participants and in all-comer participants.	• Clearance and area under the concentration-time curve (AUC) for lenvatinib.
Exploratory	
• CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

4.1.2 Treatment Period

The Treatment Period begins at the time of randomization and will end with the completion of the EOT visit

Participants will receive study treatment as continuous 21-day cycles (for participants treated with lenvatinib plus pembrolizumab and doxorubicin as the TPC choice), or continuous 28-day cycles (for participants receiving weekly paclitaxel as the TPC choice). Participants will undergo safety and efficacy assessments as defined in the SoA (Section 1.3.1).

Participants will continue to receive study treatment until disease progression is confirmed by BICR, development of unacceptable toxicity, withdrawal of consent, receipt of 35 administrations of pembrolizumab (approximately 2 years), or a lifetime cumulative dose of 500 mg/m² of doxorubicin. Discontinuation of pembrolizumab treatment may be considered for participants who have attained a confirmed CR, have been treated for at least 8 cycles (at least 24 weeks) with pembrolizumab, and had at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared. Participants who stop study treatment after receiving 35 administrations of pembrolizumab for reasons other than disease progression or intolerability, or participants who attain a CR and stop pembrolizumab may be eligible for up to an additional year of treatment with pembrolizumab (17 cycles) ± lenvatinib upon experiencing disease progression (Second Course Phase; Section 6.6.5). Participants who complete treatment with pembrolizumab after 35 cycles (approximately 2 years) or CR will continue to receive lenvatinib alone until disease progression is confirmed by BICR, development of unacceptable toxicity, or withdrawal of consent.

Participants will be permitted to continue study treatment beyond RECIST 1.1-defined disease progression as long as the maximum dose of the study drugs have not been reached (e.g. 35 administrations of pembrolizumab or a lifetime cumulative dose of 500 mg/m² of doxorubicin), the treating investigator considers that the participant may experience clinical benefit with continued treatment, and, the participant is tolerating study treatment (Section 8.2.1.6 and Appendix 5). All decisions to continue treatment beyond 2 consecutive scans showing progression at least 4 weeks apart must be discussed with the MSD Medical Monitor.

Disease progression (per RECIST 1.1) must be confirmed by BICR by the central imaging vendor (CIV) prior to the investigator discontinuing study treatment for a participant. In situations where the investigator judges that alternative treatments must be instituted immediately for a participant's safety study drug may be discontinued without waiting for confirmation of radiographic evidence of disease progression by BICR. In these cases, the investigator should consult with MSD before discontinuation of the participant from study treatment, if possible.

4.1.3 Crossover for Participants in TPC Arm to Lenvatinib 20 mg QD plus Pembrolizumab 200 mg Q3W Arm

The study's interim analysis results demonstrated that lenvatinib 20 mg QD plus pembrolizumab 200 mg Q3W was associated with superior overall survival (OS) compared to the TPC arm (investigator's choice: doxorubicin or paclitaxel) in the overall study population. Based on the positive outcome of the OS analysis, participants in the TPC arm,

4.3 Justification for Dose

4.3.1 Lenvatinib

The dosing regimen of lenvatinib for Arm A was selected based on the results of the Phase 1b/2 Study 111/KEYNOTE-146, the primary endpoint of which was to determine the MTD and RP2D for lenvatinib in combination with pembrolizumab 200 mg Q3W. Thirteen participants (lenvatinib 24 mg/day + pembrolizumab 200 mg IV Q3W: n=3; lenvatinib 20 mg/day + pembrolizumab 200 mg: n=10) were enrolled in the Phase 1b portion of the study. Eight of the participants had RCC, 2 had NSCLC, 2 had EC, and 1 had melanoma. There were 2 dose-limiting toxicities (DLTs) at the dose of lenvatinib 24 mg/day + pembrolizumab 200 mg IV Q3W (1 participant had Grade 3 arthralgia and another had Grade 3 fatigue); hence, this was defined as the toxic dose. No DLTs were reported in the next 10 participants (expansion part), all of whom received the lenvatinib 20 mg/day plus pembrolizumab 200 mg Q3W dose.

Based on the promising antitumor efficacy and tolerable safety profile seen in both the endometrial carcinoma and RCC expansion cohorts from Study 111/KEYNOTE-146 [Makker, V., et al 2018], three Phase 3 studies have been initiated for both of these tumor types, Study E7080-G000-309/KEYNOTE-775, Study E7080-G000-307/KEYNOTE-581, and LEAP-001.

4.3.2 Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg Q3W. Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W,
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically based PK [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q3W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure.

final dose of study drug will be recorded. Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded. Any medication that is considered necessary for the participant's health and that is not expected to interfere with the evaluation of or interact with the study medication may be continued during the study.

6.5.1 Allowed Concomitant Medication

Treatment of complications or AEs, or therapy to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics, and anti-diarrheal drugs), may be given at the discretion of the investigator, unless it is expected to interfere with the evaluation of (or to interact with) the study medication. Anti-emetic or any other prophylaxis should be considered in accordance with institutional guidelines.

The following concomitant medications are also allowed:

- Hormone replacement therapy
- Thyroid hormone suppressive therapy
- Adjuvant hormonal therapy for history of definitely treated breast cancer
- Anticoagulants including low molecular weight heparin (LMWH), warfarin, anti-Xa agents
- Anti-inflammatory agents
- Bisphosphonates or denosumab
- Antihypertensive therapy (including additional antihypertensive treatment as appropriate if BP increases once the participant is enrolled)
- Palliative radiotherapy to non-target bone metastases or brain lesions may be permitted after consultation with MSD

Any additional procedural or participant-specific particularities should be discussed with the investigator and MSD.

6.5.2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase of this study:

- Concurrent anticancer therapies such as chemotherapy, targeted therapies (e.g. tyrosine kinase inhibitors), hormonal therapy directed at EC, radiotherapy (with the exception of palliative radiotherapy as specified in Section 6.5.1), antitumor interventions (surgical resection, surgical debulking of tumor, etc.), or cancer immunotherapy
- Other concurrent investigational drugs
- Live vaccines within 30 days and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed.

6.6.2 Pembrolizumab

6.6.2.1 Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 4.

Participants must have measurable disease according to RECIST 1.1 as defined in Eligibility Criteria. Participants must also fulfill the medical and physical characteristics identified in the inclusion criteria and not otherwise meet any of the exclusion criteria.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 30 days before the first dose of study medication.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization. Each participant will be assigned only one screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/re-screening) are provided in Section 8.12.1.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

8.1.8 Treatment Administration

Study treatments will be administered by the investigator and/or study staff according to the specifications within the pharmacy manual. Lenvatinib may be administered at home except on Day 1 of Cycle 1 and Cycle 2. Please refer to Section 8.1.8.1.1 for further detail.

Lenvatinib may be also be administered at home during the Crossover Treatment Phase except on Day 1 of Cycle 1 and Cycle 2.

Lenvatinib compliance will be calculated by the Sponsor based on the drug accountability documented by the site staff and monitored by the Sponsor/designee. The objective is 100% compliance and investigators and their staff should evaluate compliance at each visit and take appropriate steps to optimize compliance.

CCI [redacted]

For participants in the Crossover Phase, on study imaging will be performed every 12 weeks (84 ±7 days) from first dose of Crossover study treatment or more frequently, if clinically indicated. Local reading of imaging (investigator assessment with site radiology reading) will be used for participant management. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. The same imaging technique should be used in a participant throughout the trial. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management. Bone and/or brain imaging should be performed per the SoA in section 1.3.3, as appropriate. During the Crossover Phase, imaging scans do not need to be sent to the CIV.

8.2.1.2.1 Bone Imaging During the Study

A bone scan (^{99}m-technetium-based scintigraphy, whole body bone MRI, or ^{18}F-sodium fluoride positron emission tomography [NaF PET]) at screening will only be performed in participants who have a history of bone metastases or are clinically symptomatic. The screening bone scan should be performed within 6 weeks prior to randomization (historical is acceptable). Subsequent bone scans in these participants will be performed every 24 weeks (±7 days) after randomization, or as clinically indicated, and within a target of 1 week but no more than 2 weeks following a CR as assessed by the investigator.

8.2.1.2.2 Brain Imaging During the Study

A brain scan (CT of the brain with contrast or MRI of the brain pre- and post-gadolinium) at screening will only be performed in participants who have a history of protocol-eligible brain metastases or are clinically symptomatic. Subsequent brain scans in these participants will be performed every 8 weeks (±7 days) after randomization, or as clinically indicated thereafter, and within a target of 1 week but no more than 2 weeks following achievement of a CR as assessed by the investigator.

8.2.1.3 End of Treatment and Follow-up Tumor Imaging

For participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. CCI [redacted]

For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment (Q8W) until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

recumbent position for a period of 5 minutes prior to the ECG. The Fridericia correction method for calculating QTc will be used.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Appendix 3) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the appropriate CRF.

QTc prolongation has been seen in some lenvatinib studies. Monitor electrocardiograms every cycle (as specified in the SoA) in participants with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Refer to the lenvatinib IB.

8.3.4 Echocardiogram or Multiple Gated Acquisition Scan

A MUGA scan (using technetium-based tracer) or an echocardiogram will be performed to assess left ventricular ejection fraction (LVEF) as designated in the SoA (Section 1.3.1, Section 1.3.2, and Section 1.3.3). MUGA or echocardiogram scans should be performed locally in accordance with the institution's standard practice. MUGA scans are the preferred modality; however, whichever modality is used for an individual participant at baseline should be repeated for all subsequent LVEF assessments for that participant. LVEFs as assessed by the institution will be entered onto the CRF. Investigator assessment will be based upon institutional reports.

8.3.5 Clinical Safety Laboratory Assessments

Refer to Appendix 4 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 4, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

Table 7 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Time Period			Time Frame to Report Event and Follow-up Information to MSD:
	Consent to Randomization/ Allocation	**Randomization/ Allocation through Protocol-Specified Follow-up Period**	**After the Protocol Specified Follow-up Period**	
Non-Serious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential drug-induced liver injury (DILI) - Require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (Do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

CCI [redacted]

8.10 Future Biomedical Research Sample Collection

Future biomedical research samples will not be collected in this study.

8.11 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data, associated with medical encounters, will be collected in the CRF by the investigator and study site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

All-cause hospitalizations and emergency room visits, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment, if the participant initiates new anticancer therapy, whichever is earlier.

8.12 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided above in Section 8.

8.12.1 Screening

Approximately 28 days prior to treatment randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of study treatment except for the following:

a. Laboratory tests are to be performed within 7 days prior to the first dose of study treatment. An exception is hepatitis and HIV testing which may be done up to 28 days prior to the first dose of study treatment if required by the local health authority. Repeated laboratory evaluation to establish eligibility is not allowed unless discussed and agreed upon with MSD. Refer to Appendix 9 for country-specific requirements.

b. Evaluation of ECOG is to be performed within 7 days prior to the date of first dose of study treatment.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan (SAP) are summarized here. The comprehensive plan is provided in Sections 9.2 through 9.12.

Study Design Overview	A Multicenter, Open label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Pembrolizumab Versus Treatment of Physician's Choice in Participants with Advanced Endometrial Cancer
Treatment Assignment	Approximately 780 eligible participants (660 mismatch repair proficient [pMMR] participants and 120 MMR deficient [dMMR] participants) will be randomized to one of the following 2 treatment arms in a 1:1 ratio: • Arm A: lenvatinib 20 mg (orally, QD) plus pembrolizumab 200 mg (IV Q3W) • Arm B: TPC consisting of either doxorubicin 60 mg/m^2 Q3W, or paclitaxel 80 mg/m^2 given weekly, 3 weeks on/1 week off Randomization will follow a predefined randomization scheme based on the following stratification factors: MMR status (pMMR or dMMR), ECOG performance status (0 or 1), geographic region (Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel or Region 2: rest of the world), and prior history of pelvic radiation (yes or no). First, participants will be stratified according to MMR status. Then, only within the pMMR stratum, participants will be further stratified according to ECOG performance status, geographic region, and prior history of pelvic radiation. A total of 9 strata will be utilized for the study.
Analysis Populations	Efficacy: Intention to Treat (ITT) Safety: All Participants as Treated (APaT)
Primary Endpoints	• Progression-free survival (PFS) based on RECIST 1.1 as assessed by BICR. • Overall survival (OS).
Secondary Endpoints	• Objective response rate (ORR) by BICR using RECIST 1.1. • Health-Related Quality of Life using the EORTC QLQ-C30. • Safety and tolerability of the two treatment groups. • Plasma concentration of lenvatinib versus time. • Model-predicted clearance and AUC for lenvatinib.
Statistical Methods for Key Efficacy Analyses	The primary hypotheses will be evaluated by comparing in PFS and OS using a stratified Log-rank test. The hazard ratio (HR) will be estimated using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. There are no events of interest that warrant elevation to Tier 1 events in this study. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals (CIs) provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. The 95% CIs for the between-treatment differences in percentages will be provided using the Miettinen and Nurminen method.

9.5.3 Health-Related Quality of Life Analysis Population

The HRQoL analyses are based on the HRQoL full analysis set (FAS) population, defined as participants who have received treatment and have at least one HRQoL assessment available.

9.5.4 Population Pharmacokinetic Analysis Set

The Population Pharmacokinetic Analysis Set includes all the participants who have received at least 1 dose of study treatment with documented dosing history in the lenvatinib plus pembrolizumab arm (Arm A), and have measurable plasma levels of lenvatinib.

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the sSAP.

Efficacy results for pMMR participants and all-comer participants that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 9.8 – Multiplicity. Nominal p-values will be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity.

9.6.1.1 Primary Efficacy Analysis

Progression-free Survival

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test (based on the stratification factors defined in Section 6.3.1.1). A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (Section 6.3.1.1) will be applied to both the stratified log-rank test and the stratified Cox model.

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the primary analysis, for the participants who have PD, the true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1 (based on BICR), regardless of discontinuation of study drug. Death is always considered as a confirmed PD event.

For the primary analysis, any participant who experiences an event (PD or death) immediately after 2 or more missed disease assessments will be censored at the last disease assessment prior to the missed visits. In addition, any participant who initiates new anticancer therapy prior to documented progression will be censored at the last disease assessment prior to the initiation of new anticancer therapy. Participants who do not start new anticancer therapy and who do not experience an event will be censored at the last disease

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Following initiation of treatment additional pregnancy testing will be performed as indicated in Section 1.3 during the treatment period and at least every 30 days up to 120 days after the last dose of study treatment and as required locally. Refer to Appendix 9 for country-specific requirements.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

e. Is a congenital anomaly/birth defect

- in offspring of participant taking the product regardless of time to diagnosis

f. Other important medical events:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Additional Events Reported in the Same Manner as SAE

Additional events which require reporting in the same manner as SAE

- In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to MSD in the same time frame as SAEs to meet certain local requirements. Therefore, these events are considered serious by MSD for collection purposes.
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to MSD in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by MSD. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to MSD.

- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of study treatment? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?
- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
- **Dechallenge:** Was study treatment discontinued or dose/exposure/frequency reduced?
  - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
  - If no, this is a negative dechallenge.

  (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of study treatment; (3) the study is a single-dose drug study; or (4) study treatment(s) is/are only used one time.)
- **Rechallenge:** Was the participant re-exposed to study treatment in this study?
  - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
  - If no, this is a negative rechallenge.

  (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) study treatment(s) is/are used only one time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY STUDY TREATMENT, OR IF RE-EXPOSURE TO STUDY TREATMENT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE MSD CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INIRB/IEC.

- **Consistency with Study treatment Profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study treatment or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

Table 13 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils		
Chemistry	Carbon dioxide (CO_2 or bicarbonate)[a]	Calcium	Chloride	Magnesium
	Phosphorus	Potassium	Sodium	
	Alanine aminotransferase (ALT) / Serum Glutamic Pyruvic Transaminase (SGPT)	Aspartate aminotransferase (AST) / Serum Glutamic Oxaloacetic Transaminase (SGOT)	Alkaline phosphatase	Total bilirubin (and direct bilirubin if total bilirubin is elevated above the upper limit of normal)
	Blood urea nitrogen or urea[b]	Creatinine	Thyroid stimulating hormone[c]	Free thyroxine (FT4)[c]
	Albumin	Cholesterol	Glucose	Lactate dehydrogenase
	Total protein	Triglycerides	Amylase	Lipase[d]
	CPK[e]	Pregnancy test	Triiodothyronine (T3)[c]	
Urinalysis/Urine dipstick testing[f]	• Specific gravity • Glucose, hemoglobin or blood, ketones, pH, protein[g], by dipstick			
Other Tests	• PT/INR and aPTT/PTT[h] • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)] if required by local health authority. Refer to Appendix 9 for country-specific requirements.			

Abbreviations: aPTT = activated partial thromboplastin time; CPK = creatine phosphokinase; HIV = human immunodeficiency virus; INR = international normalized ratio; PT = Prothrombin Time; RBC = red blood cell; TSH = thyroid-stimulating hormone; WBC = white blood cell.

NOTES:

a. Performed only if considered local standard of care.
b. Blood urea nitrogen is preferred; if not available, urea may be tested.
c. Free T4, T3, and TSH levels will be performed during screening and then repeated on Day 1 of every other cycle (starting with Cycle 2), at the time of discontinuation (End of Treatment), and at the Safety-Follow-up visit. Free T3 is acceptable where T3 cannot be determined. There may be instances when sites are unable to obtain the thyroid function testing results prior to scheduled dosing. After Cycle 1, review of thyroid function test results after dosing is acceptable.
d. After Cycle 1, retrospective review of lipase results is allowed when the results are not available prior to dosing.
e. CPK isoenzymes (CK-MM and CK-MB) should be evaluated if CPK is greater than 3 × ULN.
f. If urine dipstick testing suggests a urinary tract infection, or if clinically indicated, a urine microscopy, culture, and sensitivity should be performed at the institution's laboratory.
g. If urine protein is ≥2+ (first occurrence or a subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level), then a 24-hour urine collection should be done to quantify the 24-hour urine protein excretion.
h. Performed as part of the screening assessment and as clinically indicated for participants taking anticoagulation therapy.

Investigators must document their review of each laboratory safety report.

Abbreviation	Term
IV	Intravenous(ly)
K_i	Inhibitory constant
LMWH	Low molecular weight heparin
LN	Lymph node
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MAPK	Mitogen activated protein kinase
mm Hg	Millimeters of mercury
MMR	Mismatch repair
CCI	[redacted]
MRI	Magnetic Resonance Imaging
MSD	Merck Sharp & Dohme Corp.
MSI-H	Microsatellite instability-high
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
MUGA	Multigated acquisition scan
NCI	National Cancer Institute
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non–small cell lung cancer
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PBPK	Physiologically-based pharmacokinetic
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PDGF	Platelet-derived growth factor
PFS	Progression-free survival
CCI	[redacted]
PK	Pharmacokinetic

1. Continue study drug and institute antihypertensive therapy for participants not already receiving this.
2. For those participants already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or 1 or more agents of a different class of antihypertensive should be added. Study treatment can be continued without dose modification.
3. If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted and restarted at 1 dose level reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.
   - If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg recurs on the first dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at an additional dose reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.
   - If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg recurs on the second dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at a third dose reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.
   - Additional dose reduction should be discussed with MSD.

The following guidelines should be followed for the management of Grade 4 hypertension (life-threatening consequences):

1. Institute appropriate medical management
2. Discontinue study drug

6.6.1.2 Management of Proteinuria

Regular assessment of proteinuria should be conducted as detailed in the SoA (Section 1.3). Guidelines for assessment and management of proteinuria are as follows:

Detection and Confirmation

1. Perform urine dipstick testing per the SoA (Section 1.3.1)
2. A 24-hour urine collection initiated as soon as possible and at least within 72 hours (or an immediate spot urine protein-to-creatinine ratio [UPCR] test) is required in the following situations:
   - The first (initial) occurrence of ≥2+ proteinuria on urine dipstick while the participant is receiving lenvatinib

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue [b]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab monotherapy, coformulations or IO combinations may be resumed.

[b] Events that require discontinuation include, but are not limited to: Guillain-Barre Syndrome, encephalitis, myelitis, DRESS, SJS, TEN and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

CCI