Title Page

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Protocol Title: 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

Protocol Number: 775-08/E7080-G000-309

Compound Number: MK-3475/E7080

Global Sponsor of the Study

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I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Original protocol	13-FEB-2018	Not applicable.
Amendment 01	21-MAR-2018	Germany-specific amendment to address country-specific request for HIV/HBV/HCV testing and pregnancy testing at screening.
Amendment 02	06-JUN-2018	United Kingdom-specific amendment to address country-specific requests for HIV/HBV/HCV testing at screening and contraception use.
Amendment 03	31-AUG-2018	Global protocol amendment to provide clarity with respect to the number of prior lines of treatment in order to be eligible for the study.
Amendment 04	01-OCT-2018	Germany-specific amendment to address country-specific requests for HIV/HBV/HCV testing and pregnancy testing and to incorporate changes implemented in Amendment 03 to provide clarity with respect to the number of prior lines of treatment in order to be eligible for the study.
Amendment 05	02-OCT-2018	United Kingdom-specific amendment to address country-specific requests for HIV/HBV/HCV testing and to incorporate changes implemented in Amendment 03 to provide clarity with respect to the number of prior lines of treatment in order to be eligible for the study.
Amendment 06	18-FEB-2020	Revision to the statistical analysis plan to add an interim efficacy analysis to evaluate the superiority of PFS and OS.
Amendment 07	12-JUN-2020	Revision to the statistical analysis plan to revise the timing of interim efficacy analysis following communications with health authorities.

Document	Date of Issue	Overall Rationale
Amendment 08	15-JUN-2021	To allow crossover from TPC to the lenvatinib plus pembrolizumab arm at time of progression and to remove interim analysis 2 since primary objectives already met, including the final analysis of PFS.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment [08]

Overall Rationale for the Amendment:

To allow crossover from TPC to the lenvatinib plus pembrolizumab arm at time of progression and to remove interim analysis 2 since primary objectives already met, including the final analysis of PFS.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1. Protocol Summary	Participants in the chemotherapy arm, who experience disease progression, will have the opportunity to crossover from TPC to the combination arm if inclusion/exclusion criteria with the exception of exclusions #20, #21, #24, and #28 (as defined in Sections 5.1 and 5.2).	The study's interim analysis results demonstrated that combination arm (lenvatinib 20 mg [orally, QD] plus pembrolizumab 200 mg [IV Q3W]) was associated with superior overall survival (OS), progression-free survival (PFS) and objective response rate (ORR) compared to chemotherapy arm (investigator's treatment of choice [TPC]: doxorubicin or paclitaxel) in the overall study population.
1.1 Synopsis 4.1 Overall Design	Removal of cross over language. Added language to section "Duration of Participation": Following demonstration of a survival benefit in the interim analysis, eligible participants who were randomized to Arm B (TPC) and experience disease progression may have the opportunity to crossover to lenvatinib plus pembrolizumab.	For clarity and consistency, aligning with protocol amendment update - crossover from TPC to the combination arm.

Section # and Name	Description of Change	Brief Rationale
1.2 Schema	Study design schema updated to incorporate addition of crossover phase for Arm B and footnote revised.	For clarity and consistency, aligning with protocol amendment update - crossover from TPC to the combination arm.
1.3.3 Schedule of Activities - Crossover phase for TPC arm	The addition of schedule of activities table for the crossover phase for TPC arm only.	
1.3.1 Schedule of Activities 1.3.2 Schedule of Activities 1.3.3 Schedule of Activities	Addition of following text within the 12-lead ECG section: ECG at screening, C1D1, C2D1, D1 of every 4th cycle (12 weeks) thereafter (eg, C6, C10, C14, etc.), EOT, and safety follow-up. ECG at C1D1 and C2D1 should be performed approximately 2 hours post-lenvatinib dose. For high-risk participants (as defined in Sec. 8.3.3), conduct ECG monitoring every cycle. If lenvatinib is discontinued, ECGs are only required at the EOT and Safety Follow-up visits. ECGs on C1D1 are required to be on the day of dosing for participants on both arms of the study.	Updated to align with current LEAP protocol template.
4.1.2 Treatment Period	Removal of following text: Participant crossover between treatment arms is not permitted within the study treatment periods.	For clarity and consistency.

Section # and Name	Description of Change	Brief Rationale
4.1.3 Crossover for Participants in TPC Arm to Lenvatinib 20 mg QD plus Pembrolizumab 200 mg Q3W Arm	Addition of the following section: 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, who experience investigator-defined disease progression (per RECIST 1.1), will have the opportunity to participate in the Crossover Phase, receiving lenvatinib 20 mg QD plus pembrolizumab 200 mg Q3W. Participants who have started a new anticancer therapy since last dose of study treatment or have withdrawn consent from either study treatment or efficacy follow-up are not eligible for crossover. All eligibility criteria should be met, except for exclusion criteria #20, #21, #24 and #28 (Refer to Sections 5.1 and 5.2). An overview of the study design is presented in Figure 1.	For clarity and consistency, aligning with protocol amendment update - crossover from TPC to the combination arm.
4.1.4 Efficacy Follow-up Period	The addition of the following text: If participants in the TPC arm meet the eligibility criteria and enter the Crossover phase, the procedures for Crossover phase will be followed (Section 8.2.3).	For clarity and consistency.

Section # and Name	Description of Change	Brief Rationale
4.1.6 Interim Analyses	The addition of the following text: Two interim analyses are planned. Details are described in Section 9.7. Following Amendment 08, the pre-planned IA2 is no longer required because the success criteria for the study hypotheses of PFS, OS, and ORR were met at the first interim analysis (IA1). Details are described in Section 9.7.	This is because at IA1, KEYNOTE-775 met the predefined success criteria for the primary hypotheses of PFS and OS and for the secondary hypothesis of ORR in both pMMR participants and all-comer participants.at the first interim analysis (IA1) with a data cutoff of 26-OCT-2020.
4.3.4 Maximum Dose/Exposure for This Study	The addition of the following text: The maximum dose for paclitaxel is determined by site's standard of care.	To clarify the maximum dose of paclitaxel per site SOC.
9.7.2 Efficacy Interim Analyses 9.8 Multiplicity 9.9 Sample Size and Power Calculations	Language added to clarify that pre-planned second interim analysis (IA2) will not be performed.	The pre-planned second interim analysis (IA2) is no longer required because at IA1, KEYNOTE-775 met the predefined success criteria for the primary hypotheses of PFS and OS and for the secondary hypothesis of ORR in both pMMR participants and all-comer participants.at the first interim analysis (IA1) with a data cutoff of 26-OCT-2020.

Section # and Name	Description of Change	Brief Rationale
6.6.5 Second Course Phase (Retreatment Period)	Clarified text that participants from initial treatment, in pembrolizumab +/- lenvatinib may be eligible for Second Course Phase. Added that participants in the crossover phase are not eligible to retreatment with pembrolizumab (Second Course Phase).	The change is to clarify that participants in the crossover phase are not eligible to move into second course phase.
6.6.2.1 (Table 4) Dose Modification and Toxicity Management Guidelines for Immune-Related AEs Associated with Pembrolizumab	The Dose Modification and Toxicity Management Guidelines for irAEs and table were updated.	The Dose Modification and Toxicity Management Guidelines for irAEs and table were updated as requested by the US FDA in an effort to harmonize the presentation of safety information across all FDA-approved PD-1/L-1 antibody prescribing information.

Section # and Name	Description of Change	Brief Rationale
7.1.2 Crossover Phase	The addition of new section and text for cross over phase/ following text added: Participants who were randomized to Arm B (TPC) and experienced investigator-defined disease progression per RECIST 1.1, while in the study treatment phase or after stopping treatment on study but remaining in the Efficacy Follow-up or Survival Follow-up, and have not yet started subsequent anticancer therapy or withdrawn consent (from either study treatment or follow-up phases), may be eligible for the Crossover Phase. Participants entering the Crossover Phase, provided the study is still ongoing, should meet all eligibility criteria, except exclusion criteria #20, #21, #24 and #28 (refer to Sections 5.1 and 5.2). Participants may be eligible for up to two years (35 cycles) of treatment with lenvatinib plus pembrolizumab. A Second Course Phase will not be made available for participants in the Crossover Phase. Participants who complete the Crossover phase will enter the Post-Crossover Phase. Additional details are provided in Section 1.3.3. Response or progression in the Crossover Phase will not count towards the ORR and PFS of the primary endpoint in this study.	For clarity and consistency, aligning with protocol amendment update - crossover from TPC to the combination arm.

Section # and Name	Description of Change	Brief Rationale
8.2.1.2 Tumor Imaging During the Study	Addition of the following text: For participants in the Crossover Phase, on study imaging will be performed every 12 weeks (84 ±7 days) from first dose of Crossover Phase 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 as per SoA in section 1.3.3, as appropriate. During the Crossover Phase, imaging scans do not need to be sent to the CIV.	For clarity and consistency, aligning with protocol amendment update - crossover from TPC to the combination arm.
8.12.2 Treatment period	Revision of text: Visit requirements are outlined in the SoA (Section 1.3.1, Section 1.3.2, and Section 1.3.3).	For clarity and consistency, aligning with protocol amendment update - crossover from TPC to the combination arm.

Section # and Name	Description of Change	Brief Rationale
8.12.2.1 Crossover Phase	Revision of text: Addition of new section - 8.12.2.1 Crossover Phase encompassing the following text: Participants on the TPC arm (as initial treatment) who develop investigator-assessed disease progression per RECIST 1.1 and stop receiving the investigator's treatment of choice, doxorubicin or paclitaxel, may enter the Crossover Phase to receive lenvatinib plus pembrolizumab, if all eligibility criteria are met. These participants were initially randomized to the TPC arm, taken at least one dose and subsequently discontinued treatment with doxorubicin or paclitaxel. Participants who initiate a new anticancer therapy or withdraw consent (from either study treatment, Efficacy Follow-up, or Survival Follow-up) are not eligible for crossover. Participants will have laboratory assessments while receiving study treatment as outlined in the Crossover Schedule of Activities in Section 1.3.3. The Crossover Phase of the study is only available if the study remains open and the participant meets all the required eligibility criteria, except exclusions #20, #21, #24 and #28. Inclusion and exclusion criteria are defined in Sections 5.1 and 5.2. Visit requirements are outlined in Section 1.3.3 – SoA.	For clarity and consistency, aligning with protocol amendment update - crossover from TPC to the combination arm.

Section # and Name	Description of Change	Brief Rationale
8.12.3.1 Safety Follow-up	Addition of the following text: Participants in the TPC arm who are eligible for treatment with lenvatinib plus pembrolizumab in the Crossover Phase (as described in Section 8.12.2.1) may have up to two safety follow-up visits, one after the initial Treatment Period and one after the Crossover Phase.	For clarity and consistency, aligning with protocol amendment update - crossover from TPC to the combination arm
8.12.3.2 Efficacy Follow-up	Addition of the following text: Participants in the TPC arm who have discontinued study treatment and opt to receive treatment with lenvatinib plus pembrolizumab in the Crossover Phase (according to the criteria in Section 8.12.2.1) may move from the Efficacy Follow-up Phase to the Crossover Phase, if they experience investigator-defined disease progression by RECIST 1.1. Details are provided in Section 1.3.3 – Crossover Phase for TPC Arm Only.	
8.12.3.3 Survival Follow-up Contact	Addition of the following text: 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 (Section 8.12.2.1), but have not withdrawn consent (from either study treatment or Efficacy Follow-up), or started a new anticancer therapy.	

Section # and Name	Description of Change	Brief Rationale
8.2.3 Crossover Phase Assessments and Procedures	The addition of new section and text for the crossover phase assessments and procedures.	For clarity and consistency, aligning with protocol amendment update - crossover from TPC to the combination arm.
8.4.5 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs	Removal of the following text: Any suspected endpoint that upon review is not progression of the cancer under study will be forwarded to Global Pharmacovigilance as an SAE within 24 hours of determination that the event is not progression of the cancer under study.	Updated to align with current protocol template.
8.4.5 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs	The Sponsor will ensure that unblinded aggregated efficacy endpoint events and safety data are monitored to safeguard the participants in the study.	Updated to align with current protocol template.

Section # and Name	Description of Change	Brief Rationale
9.1 Statistical Analysis plan	Addition of the following text: Following Amendment 08, the pre-planned second interim analysis (IA2) is no longer required and will not be performed. This is because the success criteria for the study hypotheses of PFS, OS, and ORR were met at the first interim analysis (IA1). The prespecified final analysis will be performed without multiplicity adjustment after approximately 526 OS events have been observed in the pMMR participants and at least 18 months after the last participant was randomized. Updated analyses may be performed during the trial at any time point to provide additional estimates with longer follow-up.	The pre-planned second interim analysis (IA2) is no longer required because the success criteria for study hypotheses of PFS, OS, and ORR were met at the first interim analysis (IA1) with a data cutoff of 26-OCT-2020.
Throughout	Minor formatting and editorial changes.	To correct formatting and editorial inconsistencies.

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1. Protocol Summary

1.1 Synopsis

Protocol Title:

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

Short Title:

Phase 3 study of lenvatinib plus pembrolizumab for advanced endometrial cancer

Objectives/Hypotheses and Endpoints:

In all randomized participants with advanced endometrial cancer:

Objective/Hypothesis	Endpoint
Primary	
• Objective: To demonstrate that lenvatinib in combination with pembrolizumab is superior to Treatment of Physician's Choice (TPC) in improving progression-free survival (PFS). Hypothesis (H1): The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by PFS in pMMR participants. Hypothesis (H4): The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by PFS in all-comer participants.	• PFS, defined as the time from date of randomization to the date of the first documentation of disease progression, as determined by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), or death from any cause (whichever occurs first).
• Objective: To demonstrate that lenvatinib in combination with pembrolizumab is superior to TPC in improving overall survival (OS). Hypothesis (H2): The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by OS in pMMR participants. Hypothesis (H5): The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by OS in all-comer participants.	• OS, defined as the time from date of randomization to date of death from any cause.

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.

• 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.

Treatment Groups and Duration:

Treatment Groups	Arm A: Lenvatinib 20 mg (orally [PO] once daily [QD]) plus pembrolizumab 200 mg (intravenously [IV] every 3 weeks [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. 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 (proficient [pMMR] or deficient [dMMR]), Eastern Cooperative Oncology Group (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.
Duration of Participation	After a screening phase of 28 days, each eligible participant will be assigned to receive study treatment until disease progression is radiographically documented and verified by BICR per RECIST 1.1, and only when clinically appropriate, confirmed by the site per CCI [redacted] unacceptable adverse event(s) (AEs), withdrawal of consent, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, noncompliance with study treatment or procedure requirements or administrative reasons requiring cessation of treatment, until the participant has received 35 administrations of pembrolizumab (approximately 2 years), or the participant has received a lifetime cumulative dose of 500 mg/m² of doxorubicin. Participants who stop study treatment after receiving 35 administrations of pembrolizumab for reasons

	other than disease progression or intolerability, or participants who attain a complete response (CR) and stop study treatment may be eligible for up to 1 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 (eg, 35 administrations of pembrolizumab or lifetime cumulative dose of 500 mg/m² of doxorubicin), if the treating investigator considers that the participant may experience clinical benefit with continued treatment, and the participant is tolerating study treatment. All decisions to continue treatment beyond 2 consecutive scans (at least 4 weeks apart) showing progression must be discussed with the MSD Medical Monitor (Section 8.2.1.6 and Appendix 5). After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 8.4. Participants who discontinue for reasons other than radiographic disease progression will have post-treatment follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1 and verified by BICR, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All participants will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study. Following demonstration of a survival benefit in the interim analysis, eligible participants who were randomized to Arm B (TPC) and experience disease progression may have the opportunity to crossover to lenvatinib plus pembrolizumab. The end of the study will be the date of data cutoff for the final analysis or the time of last participant/last treatment, whichever occurs later.

Study Governance:

Study Governance Committees	

Committee	**Included in this study?**
Steering Committee	No
Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No

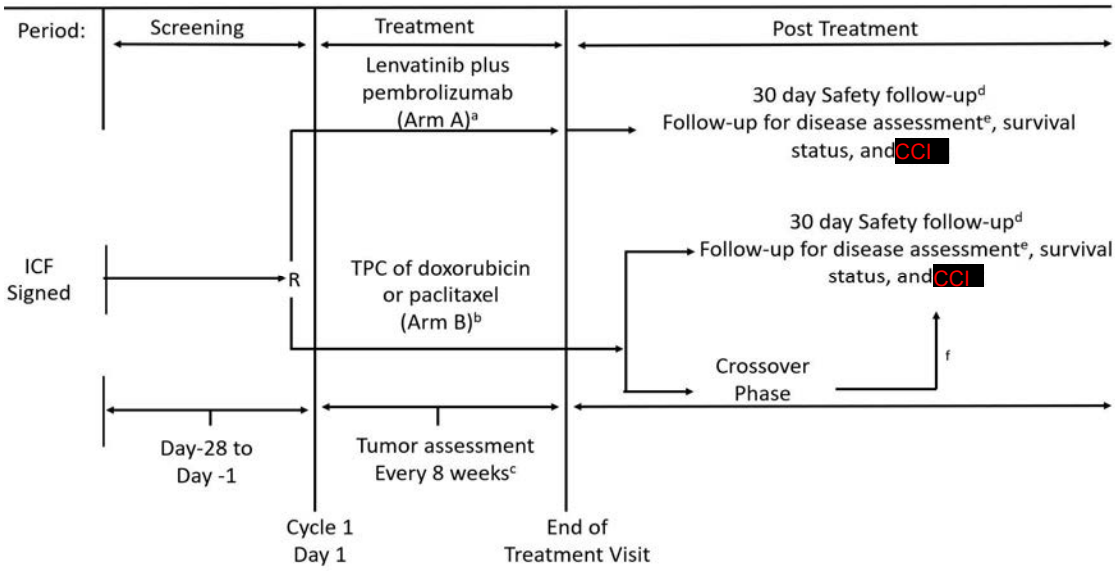
Study governance considerations are outlined in Appendix 1.

A list of abbreviations used in this document can be found in Appendix 6.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Diagram



Abbreviations: ICF = informed consent form; OS = overall survival; CCI CCI R = randomization; TPC = Treatment of Physician's Choice.

a. Lenvatinib 20 mg orally once daily plus pembrolizumab 200 mg intravenously every 3 weeks.
b. Doxorubicin 60 mg/m^2 (by intravenous bolus, 1-hour infusion, or per institutional guidelines) every 3 weeks or paclitaxel 80 mg/m^2 (by 1-hour infusion or per institutional guidelines) given weekly, 3 weeks on/1 week off.
c. Imaging to be performed Q8W from the date of randomization, or sooner if clinically indicated, until BICR-confirmation of disease progression per RECIST 1.1.
d. If End of Treatment visit occurs ≥30 days from last dose of study treatment, a safety follow-up visit is not required.
e. For participants discontinuing for reasons other than BICR-confirmed PD, tumor imaging should be performed Q8W from the date of randomization, or more frequently if clinically indicated, until BICR-confirmed PD during Efficacy Follow-up. Following the primary analysis for the study, follow-up visits and tumor assessments should be performed Q12W or more frequently if required by local standard of care.
f. Participants who were randomized to Arm B (TPC) and who experience disease progression may have the opportunity to crossover to lenvatinib plus pembrolizumab. Participants entering the crossover phase need to meet all eligibility criteria with the exception of the following exclusion criteria: #20, #21, #24 and #28.

1.3 Schedule of Activities (SoA)

1.3.1 Schedule of Activities –Treatment Period

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)**	
Administrative and General Procedures															
Informed consent	X														Consent form can be signed at any time prior to any protocol-specific screening procedures being performed. If MMR result is unavailable within 28 days from when original consent was obtained, an extension may be granted after consultation with MSD as long as all other screening procedures are performed within the protocol-specified timeframe. If the investigator plans to treat beyond disease progression, additional consent is required.
Inclusion/ exclusion	X														
Participant ID card	X														
Document TPC decision (doxorubicin or paclitaxel)	X														The proposed TPC agent that is to be given, if the participant is randomized to the TPC arm, must be selected and recorded by the investigator prior to randomization.

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	**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	**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)**	
Efficacy Procedures															
Tumor assessment – chest, abdomen and pelvis (CT/MRI)[d]	X	<---------->									X		X		Prior scans performed within the screening period but before documented informed consent is provided, may be used if consistent with protocol requirements per CIV. All imaging visits have a scheduling window of ±7 days. Imaging to be performed Q8W from the date of randomization, or sooner if clinically indicated, until BICR confirmation of disease progression per RECIST 1.1. Progression should be confirmed by BICR prior to discontinuing study treatment. For participants DCing for reasons other than BICR-confirmed PD, imaging should continue Q8W from the date of randomization until BICR-confirmed PD during Efficacy FU. Imaging at EOT is not required if the previous tumor imaging assessment was within 4 weeks prior to the EOT visit.

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)**	
Bone scan[d]	X										X				All imaging visits have a scheduling window of ±7 days. Only for participants with a history of bone metastases or who are clinically symptomatic, a bone scan will be required at screening (within 6 weeks of randomization), then Q24W, or as clinically indicated, and within 1 week, but no more than 2 weeks, of suspected CR. 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				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 at screening, at all tumor assessment time points (eg, Q8W or as clinically indicated) and within 1 week, but no more than 2 weeks, of suspected CR. Imaging at EOT is not required if the previous tumor imaging assessment was within 4 weeks prior to the EOT visit.

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)**	
Safety Procedures															
AE monitoring[c]	X	X	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.

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)**	
Vital signs (resting BP, HR, RR, and temp) and weight	X	X		X	X		X	X		X	X	X			Vital sign measurements captured on the day of randomization can be used for eligibility requirements if they are recorded prior to randomization via IRT. Participants with initial or recurrent systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored on D15 (or more frequently as clinically indicated) until systolic BP is ≤150 mm Hg and diastolic BP is ≤95 mm Hg for 2 consecutive treatment cycles. D15 visit is mandatory in C1 and C2 for all participants. During C3 and subsequent cycles, participants may return for the D15 visit if BP monitoring is required as specified above. Additional vital signs required per standard of care for the TPC arm, but not included here, should be obtained per local guidance.
Comprehensive physical examination	X			X	X			X			X				To be performed within 7 days prior to start of study treatment. A symptom-directed PE may be performed at any time during the study, as clinically indicated.
Height	X														

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)**	
NYHA	X														See Appendix 8. Only required for participants with cardiovascular impairment within 12 months of the first dose of study treatment.
12-lead ECG	X	X			X			X			X				Single 12-lead ECG. Participants must be in the recumbent position for a period of 5 minutes prior to the ECG. ECG at screening, C1D1, C2D1, D1 of every 4th cycle (12 weeks) thereafter (eg, C6, C10, C14, etc.), EOT, and safety follow-up. ECG at C1D1 and C2D1 should be performed approximately 2 hours post-lenvatinib dose. For high-risk participants (as defined in Sec. 8.3.3), conduct ECG monitoring every cycle. If lenvatinib is discontinued, ECGs are only required at the EOT and Safety Follow-up visits. ECGs on C1D1 are required to be on the day of dosing for participants on both arms of the study.

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)**	
MUGA or ECHO for LVEF assessment	X										X				Additional assessments as clinically indicated. Assessments should use the same method (MUGA or ECHO) throughout the study. MUGA or ECHO captured on the day of randomization can be used for eligibility requirements if performed and recorded prior to randomization via IRT.
Hematology and clinical chemistry laboratory assessments[e]	X			X	X		X	X			X	X			Performed locally within 7 days prior to start of treatment. Every effort should be made to collect samples at the same time of day. Hematology and clinical chemistry laboratory assessments captured on the day of randomization can be used for eligibility requirements if they are measured and results are available prior to randomization via IRT. Additional laboratory assessments required per standard of care for the TPC arm, but not included here, should be obtained per local guidance. After C1, retrospective review of lipase results is allowed when the results are not available prior to dosing.

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)**	
Urine dipstick testing	X			X	X		X	X			X	X			Performed locally within 7 days prior to start of treatment. During screening, proteinuria of >1+ requires a 24-hour urine collection. Participants with urine protein ≥1 g/24 h will not be eligible. During treatment period, repeat testing for participants with proteinuria ≥2+ should be performed on D15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles. D15 visit is mandatory in C1 and C2. During C3 and subsequent cycles, participants may return for the D15 visit if monitoring is required as specified above.
PT/INR and aPTT/PTT	X														Screening samples collected within 7 days of treatment initiation. Additional testing to be conducted as clinically indicated for participants taking anticoagulant therapy. PTT is acceptable at sites where aPTT is not performed.

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)**	
T3, FT4, TSH	X				X						X	X			Screening samples to be collected within 7 days of treatment initiation. Thyroid function tests will be performed every other cycle starting with Cycle 2 (eg, Cycle 4, 6, 8, etc.). Free T3 is acceptable where T3 cannot be determined. After C1, retrospective review of thyroid function testing results is allowed when the results are not available prior to dosing.
Pregnancy test (WOCBP only)	X				X			X				X	X		To be assessed within 3 days of treatment initiation. A serum or urine pregnancy test will be performed as indicated and at least every 30 days up to 120 days post last dose of study medication or the start of a new anticancer therapy, whichever comes first. Postmenopausal women who have not had menses for >12 months must have 2 FSH tests. Refer to Appendix 9 for country-specific requirements.
HIV, HBV, HCV	X														Testing is not required unless mandated by local health authority. Refer to Appendix 9 for country-specific requirements.

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)**	
ECOG performance status	X				X			X				X			To be assessed within 7 days of starting study treatment. ECOG performance status captured on the day of randomization can be used for eligibility requirements if measured and recorded prior to randomization via IRT. Should be assessed prior to dosing at treatment visits.
Patient Reported Outcomes															
HRQoL		X			X			X			X	X			Every effort should be made to administer HRQoL surveys prior to dosing and before other assessments and procedures. Participants will be asked to complete the HRQoL questionnaires for the equivalent of 4 cycle lengths (ie, either every 21 or 28 days depending on assigned treatment) following EOT visit. Completion of the HRQoL questionnaires following the EOT visit is not mandatory; however, every effort should be made to collect this information. At the EOT visit, participants should be invited to register for the Web Diary in order to receive access to the HRQoL questionnaires online. Questionnaire-completion reminders will be sent to those who register.

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)**	
PK/Pharmacodynamic/Biomarker Assessment															
MMR status	X														Archived tumor specimen from most recent biopsy or fresh sample collected prior to randomization.
Lenvatinib PK blood sample (Arm A only)		X		X	X										C1D1: 0.5-4 h and 6-10 h postdose. C1D15: predose and 2-12 h postdose. C2D1: predose, 0.5-4 h, and 6-10 h postdose. Note: all predose samples should be collected within 30 minutes of lenvatinib dosing. Note: postdose samples not needed if lenvatinib administration is skipped.
CCI [redacted]															

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)	

CCI [redacted]

Abbreviations: AE = adverse event; BICR = blinded independent central review; BP = blood pressure; C1 = Cycle 1; C2 = Cycle 2; CIV = central imaging vendor; CR = complete response; CT = computed tomography; D1 = Day 1; D15 = Day 15; D8 = Day 8; DC = discontinuation; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FIGO = International Federation of Gynecology and Obstetrics; FT4 = free thyroxine; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HR = heart rate; HRQoL = Health-Related Quality of Life; ID = identification; IEC = Independent Ethics Committee; IRB = Independent Review Board; IRT = interactive response technology; LVEF = left ventricular ejection fraction; MMR = mismatch repair; MRI = magnetic resonance imaging; MSD = Merck Sharp & Dohme Corp.; MUGA = multigated acquisition; nAb = neutralizing antibodies; NYHA = New York Heart Association; PD = progressive disease; PE = physical examination; CCI [redacted] PK = pharmacokinetics; Q3W = every 3 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; Q24W = every 24 weeks; QD = once daily; QW = every week; CCI [redacted] RR = respiratory rate; SAE = serious adverse event; T3 = triiodothyronine; TPC = treatment of physician's choice; TSH = thyroid stimulating hormone; WES = whole exome sequencing; WOCBP = women of childbearing potential.

a. Screening procedures should be performed within 28 days prior to first dose of study treatment unless there is another timeframe specified within the procedure-specific note.
b. 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.
c. For participants receiving either pembrolizumab plus lenvatinib or doxorubicin, a review of concomitant medications and AEs should be performed on Day 8 of Cycle 1; a clinic visit is not required and can be performed via a telephone-call. Following Cycle 1, the review of concomitant medications and AEs on Day 8 is not required for participants receiving either pembrolizumab plus lenvatinib or doxorubicin. The Day 8 visit is required for participants receiving paclitaxel.
d. Following the primary analysis for the study: follow-up visits and tumor assessments should be performed Q12W or more frequently if required by local standard of care. Bone and brain scans should be performed per local standard of care.
e. From C2D1 onwards, clinical laboratory assessments may be conducted up to 72 hours prior to the scheduled visit, unless otherwise specified. Procedures/assessments should be performed prior to administration of study treatment.

CCI [redacted]

1.3.2 Schedule of Activities – Second Course Phase (Retreatment)

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)**	
Administrative and General Procedures													
Inclusion/exclusion	X												
Prior/Concomitant medication review	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).
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.
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).
Survival status	←	----	----	----	----	----	----	----	----	----	----	X	Participants will be followed for survival (unless this information is not allowed to be provided due to confidentiality).
Administration of Study Treatment													
Pembrolizumab ± lenvatinib	X	X	X	X	X	X	X	X					Pembrolizumab 200 mg Q3W ± lenvatinib 20 mg QD; 21-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)**	
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	**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	**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)**	
Physical examination	X								X	X			A symptom-directed PE as clinically indicated.
12-lead ECG	X	X	X	X	X	X	X	X	X				An ECG is required prior to restarting treatment only if it was not already completed within 28 days prior. An ECG assessment prior to administration of study treatment is only required for participants who are receiving lenvatinib in the Second Course Phase. ECG at screening, C1D1, C2D1, D1 of every 4th cycle (12 weeks) thereafter (eg, C6, C10, C14, etc.), EOT, and safety follow-up. ECG at C1D1 and C2D1 should be performed approximately 2 hours post-lenvatinib dose. For high-risk participants (as defined in Sec. 8.3.3), conduct ECG monitoring every cycle. If lenvatinib is discontinued, ECGs are only required at the EOT and Safety Follow-up visits. ECGs on C1D1 are required to be on the day of dosing for participants on both arms of the study.

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)**	
MUGA or ECHO for LVEF assessment	X								X				Required prior to restarting treatment only if it was not already completed within 28 days prior. Only required if lenvatinib is administered. Additional assessments as clinically indicated. Assessment should use the same method (MUGA or ECHO) throughout the study.
Hematology and clinical chemistry	X	X	X	X	X	X	X	X	X	X			Performed locally within 3 days prior to starting second course treatment. After second course Cycle 1, may be collected up to 72 hours prior to dosing. Retrospective review of lipase results is allowed when the results are not available prior to dosing.
Urine dipstick testing	X	X	X	X	X	X	X	X	X	X			Performed locally within 3 days prior to starting second course treatment. **For participants only receiving pembrolizumab**: testing is to be performed every other cycle (eg, Cycle 1, 3, 5, etc.). **For participants receiving pembrolizumab and lenvatinib**: testing is to be performed on Day 1 of every cycle. Repeat testing for participants with initial or repeat 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.

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)**	
PT/INR and aPTT/PTT	X												Performed locally within 3 days prior to starting second course treatment. Additional testing to be conducted as clinically indicated for participants taking anticoagulant therapy. PTT is acceptable at sites where aPTT is not performed.
T3, FT4, TSH	X		X		X		X	X	X	X			Performed locally within 3 days prior to starting second course treatment, then on Day 1 of every other cycle (Cycles 3, 5, 7, etc.). Free T3 is acceptable where T3 cannot be determined. Retrospective review of thyroid function testing results is allowed when the results are not available prior to dosing.
Pregnancy test	X	X	X	X	X	X	X	X	X	X	X		A serum or urine pregnancy test will be performed in women of childbearing potential (ie, premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months) as indicated and at least every 30 days up to 120 days post last dose of study medication or the start of a new anticancer therapy, whichever comes first. Postmenopausal women who have not had menses for >12 months must have 2 FSH tests.

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)**	
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X		Performed within 7 days prior to starting second course treatment

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; BP = blood pressure; C1 = Cycle 1; C2 = Cycle 2; CT = computed tomography; D1 = Day 1; D15 = Day 15; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; FT4 = free thyroxine; HR = heart rate; INR = international normalized ratio; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PD = progressive disease; PE = physical examination; CCI PT = prothrombin time; Q3W = every 3 weeks; RR = respiratory rate; T3 = triiodothyronine; TSH = thyroid stimulating hormone; SAE = serious adverse event.

1.3.3 Schedule of Activities – Crossover Phase for TPC Arm Only

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)**	
Administrative and General Procedures															
Inclusion/ exclusion	X														
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).
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.
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).

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.

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.

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)**	
Safety Procedures															
AE monitoring[c]	X	X	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			Participants with initial or recurrent systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored on D15 (or more frequently as clinically indicated) until systolic BP is ≤150 mm Hg and diastolic BP is ≤95 mm Hg for 2 consecutive treatment cycles. D15 visit is mandatory in C1 and C2 for all participants. During C3 and subsequent cycles, participants may return for the D15 visit if BP monitoring is required as specified above.

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)	
12-lead ECG	X	X			X			X			X				Single 12-lead ECG. Participants must be in the recumbent position for a period of 5 minutes prior to the ECG. ECG at screening, C1D1, C2D1, D1 of every 4th cycle (12 weeks) thereafter (eg, C6, C10, C14, etc.), EOT, and safety follow-up. ECG at C1D1 and C2D1 should be performed approximately 2 hours post-lenvatinib dose. For high-risk participants (as defined in Sec. 8.3.3), conduct ECG monitoring every cycle. If lenvatinib is discontinued, ECGs are only required at the EOT and Safety Follow-up visits. ECGs on C1D1 are required to be on the day of dosing for participants on both arms of the study
MUGA or ECHO for LVEF assessment	X										X				Required prior to restarting crossover phase only if it was not already completed within 28 days prior. Additional assessments as clinically indicated. Assessments should use the same method (MUGA or ECHO) throughout the study.

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)**	
Hematology and clinical chemistry laboratory assessments[e]	X			X	X		X	X			X	X			Performed locally within 7 days prior to start of crossover phase. Every effort should be made to collect samples at the same time of day. After C1, retrospective review of lipase results is allowed when the results are not available prior to dosing.
Urine dipstick testing	X			X	X		X	X			X	X			Performed locally within 7 days prior to start of treatment. Participants with urine protein ≥1 g/24 h will not be eligible. During crossover phase, repeat testing for participants with proteinuria ≥2+ should be performed on D15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles. D15 visit is mandatory in C1 and C2. During C3 and subsequent cycles, participants may return for the D15 visit if monitoring is required as specified above.

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)**	
PT/INR and aPTT/PTT	X														Eligibility samples collected within 7 days of crossover phase initiation. Additional testing to be conducted as clinically indicated for participants taking anticoagulant therapy. PTT is acceptable at sites where aPTT is not performed.
T3, FT4, TSH	X				X						X	X			Eligibility samples to be collected within 7 days of crossover phase initiation. Thyroid function tests will be performed every other cycle starting with Cycle 2 (eg, Cycle 4, 6, 8, etc.). Free T3 is acceptable where T3 cannot be determined. After C1, retrospective review of thyroid function testing results is allowed when the results are not available prior to dosing.

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)**	
Pregnancy test (WOCBP only)	X				X			X				X	X		To be assessed within 3 days of crossover phase initiation. A serum or urine pregnancy test will be performed as indicated and at least every 30 days up to 120 days post last dose of study medication or the start of a new anticancer therapy, whichever comes first. Postmenopausal women who have not had menses for >12 months must have 2 FSH tests. Refer to Appendix 9 for country-specific requirements.
ECOG performance status	X				X			X				X			To be assessed within 7 days of starting crossover phase for eligibility requirement. Should be assessed prior to dosing at treatment visits.

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)	

Abbreviations: AE = adverse event; BP = blood pressure; C1 = Cycle 1; C2 = Cycle 2; CR = complete response; CT = computed tomography; D1 = Day 1; D15 = Day 15; D8 = Day 8; DC = discontinuation; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FT4 = free thyroxine; HR = heart rate; IEC = Independent Ethics Committee; IRB = Independent Review Board; IRT = interactive response technology; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MSD = Merck Sharp & Dohme Corp.; MUGA = multigated acquisition; PD = progressive disease; PE = physical examination; CCI [redacted] Q3W = every 3 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; Q24W = every 24 weeks; QD = once daily; QW = every week; RR = respiratory rate; SAE = serious adverse event; T3 = triiodothyronine; TSH = thyroid stimulating hormone; WOCBP = women of childbearing potential.

a. Eligibility procedures should be performed within 28 days prior to first dose of crossover phase unless there is another timeframe specified within the procedure-specific note.
b. If EOT visit occurs ≥30 days from last dose of crossover phase, 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.
c. For participants receiving pembrolizumab plus lenvatinib, a review of concomitant medications and AEs should be performed on Day 8 of Cycle 1; a clinic visit is not required and can be performed via a telephone-call. Following Cycle 1, the review of concomitant medications and AEs on Day 8 is not required for participants receiving pembrolizumab plus lenvatinib.
d. Following the primary analysis for the study: follow-up visits and tumor assessments should be performed Q12W or more frequently if required by local standard of care. Bone and brain scans should be performed per local standard of care.
e. From C2D1 onwards, clinical laboratory assessments may be conducted up to 72 hours prior to the scheduled visit, unless otherwise specified. Procedures/assessments should be performed prior to administration of crossover study treatment.

2. Introduction

2.1 Study Rationale

2.1.1 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death 1 ligand 1 (PD-L1) and programmed cell death 1 ligand 2 (PD-L2). Lenvatinib (also known as E7080 or MK-7902) inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib inhibits other kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; platelet-derived growth factor receptor alpha (PDGFRα), KIT, and RET. Lenvatinib also exhibited antiproliferative activity in cell lines dependent on activated FGFR signaling with a concurrent inhibition of FGF-receptor substrate 2α phosphorylation. Pembrolizumab combined with once daily (QD) dosing of lenvatinib is currently being developed for the treatment of advanced endometrial cancer.

Refer to the respective Investigator's Brochure (IB) for detailed background information on pembrolizumab and lenvatinib.

2.1.2 Pharmaceutical and Therapeutic Background

2.1.2.1 Lenvatinib

Angiogenesis, the formation of new blood vessels from a pre-existing vascular network, is essential for tumor growth and metastasis. VEGF and its family of receptors (VEGRs 1-3) play a major role in tumor angiogenesis [Ferrara, N., et al 2003] [Ellis, L. M. 2008] [Tammela, T. 2010]. Accumulated evidence suggests that FGF and its receptor tyrosine kinase, FGFR also play important roles for tumor angiogenesis [Cross, M. J. 2001] [Lieu, C., et al 2011] [Limaverde-Sousa, G., et al 2014].

Lenvatinib is a potent multiple RTK inhibitor that selectively inhibits VEGF receptors, VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), FGFR1-4, PDGFRα, KIT, and RET. Among known kinase inhibitors in clinical use, lenvatinib is one of the only inhibitors currently labeled with a mechanism of action as an inhibitor of not only VEGFRs but also FGFRs, both of which are currently believed to be very important for tumor angiogenesis.

Lenvatinib inhibited cell-free kinase activities for VEGFR1-3 and FGFR1-3 with K_i values around 1 nmol/L, and 8-22 nmol/L, respectively. In cell-based assays, lenvatinib inhibited VEGF-derived and FGF-derived tube formation of human umbilical vein endothelial cells (HUVEC) with IC_{50} values of 2.1 and 7.3 nmol/L, respectively. Analysis of the signal transduction molecules revealed that lenvatinib inhibited both the mitogen activated protein kinase (MAPK) pathway and the mammalian target of rapamycin (mTOR)-S6 kinase (S6K)-S6 pathway in HUVECs triggered by activated VEGFR and FGFR. Furthermore, lenvatinib (10, 30 mg/kg) significantly inhibited both VEGF- and FGF-driven angiogenesis in a murine in vivo model [Yamamoto, Y., et al 2014]. In vivo, lenvatinib exhibited antitumor activity

against various human tumor xenografts in athymic mice including 5 types of thyroid carcinomas (differentiated [papillary and follicular], anaplastic, squamous, and medullary thyroid carcinomas), renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), melanoma, gastric cancer, non–small cell lung cancer (NSCLC), ovarian cancer, Ewing's sarcoma, and osteosarcoma. In addition, the antitumor activity of lenvatinib in combination with other anticancer agents in several xenograft models was greater than that of lenvatinib or the other agents alone.

In summary, lenvatinib inhibited VEGF-driven VEGFR2 phosphorylation and suppressed proliferation and tube formation in HUVEC models. Antitumor activity of lenvatinib in vivo has been shown in numerous xenograft animals. These results suggest that lenvatinib may be a novel anticancer therapy through inhibition of angiogenesis and may be useful as either monotherapy or in combination with other anticancer drugs.

2.1.2.2 Pembrolizumab

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, M. L. 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of cluster of differentiation 8 positive (CD8+) T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and RCC. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005]

[Francisco, L. M., et al 2010]. As a consequence, the PD 1/PD-L1 pathway is an attractive target for therapeutic intervention in endometrial cancer (EC).

2.1.2.3 Endometrial Cancer: Epidemiology and Current Therapeutic Options

Endometrial cancer is the fifth most common cancer in women worldwide, with approximately 320,000 new cases diagnosed in 2012 [Ferlay, J., et al 2015]. In the United States, the estimated numbers of new cases and deaths occurring in 2017 are 61,380 and 10,920, respectively. A majority of EC cases are identified at an early stage with a 5-year survival rate of 95.3% for localized EC [National Cancer Institute 2017]. However, despite early detection, approximately 13% of all endometrial cancers recur [Fung-Kee-Fung, M., et al 2006]. In general, for patients with advanced or recurrent EC, median survival is only approximately 12 months [Obel, J. C., et al 2006].

For patients presenting with advanced disease, treatment options are limited with no consensus on a standard regimen. Chemotherapy has been the standard of care in the first-line treatment of EC, with platinum compounds, anthracyclines, and taxanes being the most commonly used, alone and in combination [National Comprehensive Cancer Network 2017] [Colombo, N., et al 2013]. Cytotoxic therapy is also a de facto standard in second-line treatment; however, response rates are low, progression-free survival (PFS) and overall survival (OS) are short, and no drug has proven to be effective. To date, studies in this setting have shown response rates of 15% or lower with median OS and PFS of approximately 12 months and 4 months, respectively [McMeekin, S., et al 2015]. Given the unmet clinical need in this patient population, exploration of novel therapeutic approaches is warranted.

The proposed multicenter, randomized, open-label, Phase 3 study (KEYNOTE-775/E7080-G000-309, hereafter referred to as “Study 309”) will compare the efficacy and safety of lenvatinib in combination with pembrolizumab versus treatment of physician’s choice (TPC) in participants with advanced EC.

2.1.2.4 Scientific Rationale for the Combination of Lenvatinib with Pembrolizumab

In preclinical models, lenvatinib decreased the tumor associated macrophage (TAM) population, which is known as an immune-regulator in the tumor microenvironment. The decrease in TAM population was accompanied by increases in activated cytotoxic T-cell populations through stimulation of interferon-gamma signaling, resulting in increased immune activation [Kimura, T., et al 2018]. The immune-modulating effect of lenvatinib may result in a potent combination effect with PD-1/PD-L1 signal inhibitors. The effect of combining lenvatinib with an anti-human PD-1 humanized mAb was investigated in 4 murine tumor isograft models, which showed significant tumor growth inhibition compared to control. In the RAG murine tumor isograft tumor model, survival in the group treated with the combination was significantly longer than that of the respective monotherapy groups. In the CT26 murine tumor isograft model, treatment with the combination significantly increased the population of activated cytotoxic T-cells compared to that of the respective monotherapy groups [Kato, Y., et al 2019]. All treatments were well tolerated, and severe body weight loss was not observed.

2.1.2.5 Clinical Data on Lenvatinib in Combination with Pembrolizumab for Treatment of EC

Promising activity was observed in 53 EC participants analyzed for efficacy and safety during an interim analysis of the Phase 2 Study 111/KEYNOTE-146; all participants initiated treatment at the 20 mg lenvatinib QD + 200 mg pembrolizumab IV Q3W dosing level [Makker, V., et al 2018]. The EC participants were predominantly Caucasian (83%), with a median age of 63.7 years, and all had an ECOG performance status score of 0 (38%) or 1 (62%). All participants had received prior anticancer therapy regimens (1 prior [42%], 2 prior [42%], ≥3 prior [17%]). At baseline, 85% of participants had microsatellite stable (MSS) tumors, 7.5% had microsatellite instability (MSI)-high (MSI-H) tumors, and 7.5% of participants had an unknown MSI status. Thirteen participants (24.5%) were PD-L1 positive, 11 (20.8%) were PD-L1 negative, and 29 (54.7%) were not tested for PD-L1 status.

The best overall response (BOR) was evaluated per immune-related Response Evaluation Criteria for Solid Tumors (irRECIST) by both investigator assessment and independent radiology review (IRR). As of the 15-DEC-2017 data cutoff, the BOR by investigator assessment included 1 CR (1.9%), 20 PR (37.7%) and 25 SD (47.2%). The BOR as assessed by independent radiology review (3 CR [5.7%], 22 PR [41.5%], and 19 SD [35.8%]) was comparable to the BOR by investigator assessment.

By investigator assessment, the primary endpoint of objective response rate (ORR) at Week 24 (ORR_{Week24}) was equal to the overall ORR (39.6% [21/53; 95% CI: 26.5–54.0]). Comparable ORRs were observed in subgroups of participants with MSI-H tumors (2/4 [50.0%]; 95% CI: 6.8–93.2) versus those with MSS tumors (16/45 [35.6%]; 95% CI: 21.9–51.2). CCI [redacted] Secondary analysis of tumor efficacy by IRR showed an ORR_{Week24} of 45.3% and an overall ORR of 47.2%. Median PFS by investigator assessment per irRECIST was 7.4 months (95% CI: 5.0-not estimable).

Treatment with lenvatinib plus pembrolizumab was associated with an acceptable safety profile in this patient population. Toxicities were generally manageable with supportive medications, dose interruptions, and/or lenvatinib dose reductions. The most frequently reported treatment-related AEs (any grade) were hypertension (59%), fatigue (55%), diarrhea (51%), hypothyroidism (47%), and decreased appetite (40%). Of the 5 deaths that occurred in this study, only 1 death (caused by an AE of intracranial hemorrhage) was considered related to the study intervention by the investigator.

2.1.2.6 Clinical Data on Lenvatinib and Pembrolizumab as Single Agents for the Treatment of EC

Eisai and MSD have conducted studies of lenvatinib and pembrolizumab as single agents, respectively, in the treatment of advanced EC.

Eisai has conducted a Phase 2 open-label, single-arm study of lenvatinib monotherapy in advanced EC following first-line platinum-based chemotherapy with 133 treated participants (E7080-G000-204). The primary endpoint was ORR, based on RECIST 1.1, as determined by independent radiologic review (IRR). Per IRR, 19 (14.3%) participants achieved a best overall response of either complete response (CR; 1 participant) or PR (18 participants), and

per investigator assessment, 28 (21.1%) participants achieved either CR (2 participants) or PR (26 participants). The median PFS was 5.6 months based on IRR assessment and was 5.4 months based on investigator assessment. For the responders, the median duration of response was 7.2 months based on IRR assessment and 8.0 months based on investigator assessment. Median OS was 10.6 months with a median duration of follow-up of 15.2 months (Eisai Data on File).

Most participants experienced at least 1 treatment-emergent AE (TEAE; 126/133 participants, 94.7%) and at least 1 TEAE reported as treatment-related (116/133 participants, 87.2%). The most frequently reported TEAEs (>20% of all participants, in descending frequency) were hypertension, fatigue, diarrhea, decreased appetite, nausea, abdominal pain, headache, asthenia, vomiting, stomatitis, proteinuria, dysphonia and weight decreased. The most commonly reported TEAEs reported as treatment-related (>20% of participants, in order of descending frequency) were as follows: hypertension, fatigue, decreased appetite, diarrhea, headache, nausea, proteinuria, and stomatitis. TEAEs that were Grade 3 or above (severe) occurred in 97 (72.9%) participants; this includes 14 participants (10.5%) with Grade 5 events. Among the 14 Grade 5 SAEs, 6 of these were also associated with disease progression. Observed toxicities were consistent with previously reported events associated with lenvatinib and other drugs that target the VEGFR (Eisai Data on File).

MSD has conducted a Phase 1b study evaluating pembrolizumab monotherapy (10 mg/kg administered IV every 2 weeks [Q2W]) in 24 participants with PD-L1 positive advanced EC, including 22 participants who received 1 or more prior lines of therapy for advanced disease (KEYNOTE-028 [KN028], NCT02054806). At the time of the data cutoff (17-FEB-2016), the ORR, based on RECIST 1.1, was 13% (n=3), and median PFS observed was 1.8 months with 6- and 12-month PFS rates of 19.0% and 14.3%, respectively. CCI [redacted]
The median OS was not reached, and the 6- and 12-month OS rates were 67.0% and 51.0%, respectively [Ott, P. A., et al 2017].

At the time of the data cutoff, the median follow-up duration was 76.2 weeks (range: 2.6 to 94.3 weeks). Thirteen participants (54.2%) experienced treatment-related AEs, with fatigue (20.8%), pruritus (16.7%), pyrexia (12.5%), and decreased appetite (12.5%) occurring in ≥10% of participants. Grade 3 treatment-related AEs were reported in 4 participants (16.7%): 1 participant had asthenia and back pain; 1 participant had anemia, hyperglycemia, and hyponatremia; 1 participant had chills and pyrexia; and 1 participant had diarrhea. No participant experienced a Grade 4 AE or immune-mediated AE of any grade, no participant discontinued treatment because of an AE, and no participant experienced treatment-related death [Ott, P. A., et al 2017].

MSD is further investigating the clinical benefit of pembrolizumab monotherapy (200 mg administered IV Q3W) for in advanced EC, regardless of PD-L1 positivity, in the multi-cohort Phase 2 KN158 (NCT02628067) study.

As of 28-APR-2017, 107 EC participants have been treated. A majority of participants (62.6%) had not received prior neoadjuvant/adjuvant therapy. Most participants had received prior therapy for recurrent/metastatic disease (1 prior [29.0%], 2 prior [27.1%], 3 or more prior [31.8%]), with 10.3% of participants receiving no prior therapy for recurrent/metastatic disease (MSD Data on File).

The ORR based on RECIST 1.1 per blinded independent central review (BICR) assessment is 11.2% (95% CI: 5.9%, 18.8%), with all 12 participants achieving a best overall response of PR. Median PFS observed was 2.1 months. CCI [redacted] The median OS was 11.1 months (MSD Data on File).

The majority of participants had at least 1 AE (n=103; 96.3%), with 64.5% (n=69) considered related to the study drug by the investigator. Grade 3, 4, or 5 events occurred in 57.9% of participants, with 15.9% considered related to the study drug by the investigator. There were 3 participants who died while on study. One death case was due to pulmonary sepsis (starting 32 days after start of treatment), 1 death was due to dyspnea (starting 45 days after start of treatment), and 1 death was due to general physical deterioration, with cardiac arrest (starting 14 days after the start of treatment). These deaths were not attributed to clinical or radiological progression. The most common AEs of any grade occurring in ≥25% of participants were decreased appetite (26.2%), nausea (29.0%), and fatigue (29.9%; MSD Data on File).

The observed toxicities of pembrolizumab monotherapy in advanced EC are consistent with previously reported events associated with pembrolizumab.

The ORR from these studies suggest that the activity observed for the combination of lenvatinib with pembrolizumab in Study 111/KEYNOTE-146 is greater than can be accounted for by each of these single agents on their own.

2.1.3 Preclinical and Clinical Studies

Refer to the respective IBs for preclinical and clinical study data for pembrolizumab and lenvatinib.

2.1.4 Ongoing Clinical Studies

Refer to the respective IBs for ongoing clinical study data for pembrolizumab and lenvatinib.

2.1.5 Information on Other Study-related Therapy

For additional information on doxorubicin and paclitaxel, refer to the respective approved product labels.

2.2 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

As discussed in Sections 2.1.2.5 and 2.1.2.6, both lenvatinib and pembrolizumab (alone and in combination), have shown promising efficacy in participants with EC. Given the short median survival [Obel, J. C., et al 2006] and limited treatment options for patients with advanced or recurrent EC, there is an unmet need for clinical need for novel therapies in this setting. The existing data suggest that inhibiting angiogenesis in combination with PD-1 blockade is a promising therapeutic strategy and the benefit:risk assessment for participants included in this study is considered to be favorable.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and Informed Consent documents.

3. Objectives/Hypotheses and Endpoints

In all randomized participants with advanced endometrial cancer:

Objective/Hypothesis	Endpoint
Primary	
• Objective: To demonstrate that lenvatinib in combination with pembrolizumab is superior to Treatment of Physician's Choice (TPC) in improving progression-free survival (PFS). Hypothesis (H1): The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by PFS in pMMR participants. Hypothesis (H4): The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by PFS in all-comer participants.	• PFS, defined as the time from date of randomization to the date of the first documentation of disease progression, as determined by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), or death from any cause, whichever occurs first.
• Objective: To demonstrate that lenvatinib in combination with pembrolizumab is superior to TPC in improving overall survival (OS). Hypothesis (H2): The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by OS in pMMR participants. Hypothesis (H5): The combination of lenvatinib and pembrolizumab is superior to TPC as assessed by OS in all-comer participants.	• OS, defined as the time from date of randomization to date of death from any cause.

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.

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]

Objective/Hypothesis	Endpoint
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

4. Study Design

4.1 Overall Design

This is a multicenter, randomized, open-label, Phase 3 study to compare the efficacy and safety of lenvatinib in combination with pembrolizumab versus TPC in participants with advanced EC who have been treated with at least 1 prior platinum-based chemotherapy regimen.

Approximately 780 eligible participants (660 mismatch repair proficient [pMMR] participants and up to 120 MMR deficient [dMMR] participants) will be randomized to 1 of

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.

4.1.2 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,

who experience investigator-defined disease progression (per RECIST 1.1), will have the opportunity to participate in the Crossover Phase, receiving lenvatinib 20 mg QD plus pembrolizumab 200 mg Q3W. Participants who have started a new anticancer therapy since last dose of study treatment or have withdrawn consent from study treatment, efficacy follow-up or survival follow-up are not eligible for crossover. All eligibility criteria should be met, except for exclusion criteria #20, #21, #24 and #28 (Refer to Sections 5.1 and 5.2).

An overview of the study design is presented in Figure 1.

4.1.4 Efficacy Follow-up Period

The Efficacy Follow-up Period will begin the day after the EOT Visit and will continue as long as the participant is alive, until the data cutoff date for the primary OS analysis, or when all participants have discontinued study treatment, unless the participant withdraws consent, or is lost to follow-up. If a participant discontinues study treatment and withdraws consent to continued follow-up, the investigator must not access confidential records that require the participant's consent. However, an investigator may consult public records to establish survival status if permitted by local regulations.

If participants in the TPC arm meet the eligibility criteria and enter the Crossover phase, the procedures for Crossover phase will be followed (Section 8.2.3).

CCI [redacted] This information will be recorded unless this information is not allowed to be provided due to confidentiality. Participants will also be asked to complete HRQoL questionnaires as outlined in Section 8.2.2.

If a participant fails to attend a scheduled assessment (eg, visit/phone), the investigator or designee will make every attempt to contact the participant to determine his or her status. All attempts at contact will be recorded in the participant's medical notes. Participants will be judged as lost to follow-up as outlined in Section 7.3.

All participants who discontinue study drug treatment prior to disease progression will continue to undergo tumor assessments every 8 weeks from the date of randomization in the Efficacy Follow-up Period until disease progression is documented and confirmed by BICR or a new anticancer therapy is initiated, unless the participant withdraws consent. Following the primary analysis for the study, tumor assessments should be performed every 12 weeks or more frequently per local standard of care.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the Schedule of Activities (SoA), Section 1.3. Details of each procedure are provided in Section 8.

4.1.5 Data Monitoring Committee

An external data monitoring committee (DMC) will be assembled and will be responsible for periodic monitoring of safety and efficacy data as well as the results from the interim analysis. The function and membership of the DMC will be described in the DMC charter.

4.1.6 Interim Analyses

Two interim analyses are planned (IA1 and IA2), but IA2 will not be performed. Following Amendment 08, the pre-planned IA2 is no longer required because the success criteria for the study hypotheses of PFS, OS, and ORR were met at the first interim analysis (IA1). Details are described in Section 9.7.

4.2 Scientific Rationale for Study Design

This multicenter, randomized, open-label, Phase 3 study was designed to compare the efficacy and safety of lenvatinib in combination with pembrolizumab versus TPC in participants with advanced EC who have been treated with at least 1 prior platinum-based chemotherapy regimen. Randomization will be used in this study to avoid bias in the assignment of participants to treatment, to increase the likelihood that known and unknown participant attributes (eg, demographics and baseline characteristics) are balanced across treatment arms, and to ensure the validity of statistical comparisons across treatment arms. Treatments will be open-labeled, since the dosage and administration is different between lenvatinib, pembrolizumab, doxorubicin, and paclitaxel.

The sample size is estimated based on the primary endpoints of PFS and OS, and the required target events to detect the superiority of lenvatinib to TPC in the comparison of PFS and OS.

4.2.1 Rationale for Patient Population

Tumors that have a large number of somatic mutations have been shown to be more susceptible to PD-1 inhibition. One mechanism that generates increased numbers of somatic mutations is through defects in MMR. MMR corrects errors that spontaneously occur during DNA replication, such as single-base mismatches, short insertions, and deletions. Tumors with defects in MMR are known to harbor hundreds to thousands of somatic mutations. Regions of repetitive DNA, known as microsatellites, are known to be particularly susceptible to these deficiencies. Although the length of these microsatellite regions is highly variable from person to person, each individual has microsatellite regions of a set length. MMR deficiency leads to the accumulation of mutations in these regions, termed microsatellite instability (MSI).

Patients with MSI-H/dMMR-mutant EC appear to have more favorable response rates to pembrolizumab alone, which was recently granted accelerated approval by the FDA for the treatment of patients with unresectable or metastatic MSI-H or dMRR tumors, including EC. In order to account for the improved efficacy of pembrolizumab in the MSI-H/dMRR EC population, the sample size will be powered for the pMMR population. Thus, the study will enroll all EC participants (both pMMR and dMMR) and the sample size would increase to account for the additional dMMR patients (an estimated 10-15% increase in sample size). The study will stop recruitment once fully enrolled for pMMR participants (n=660) and the number of participants with dMMR will be capped (n=120). The primary statistical analysis will be completed for pMMR participants first, then the entire study population (all-comers).

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.

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.

The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed-dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.3.3 Chemotherapy

Doses and regimens for TPC (Arm B; doxorubicin 60 mg/m^2 Q3W or paclitaxel 80 mg/m^2 3 weeks on/1 week off) were selected based on standard clinical practice.

4.3.4 Maximum Dose/Exposure for This Study

The maximum dose/exposure of pembrolizumab allowed in this study is 200 mg Q3W up to 2 years; however, participants may be eligible for an additional 17 administrations (1 year; Section 6.6.5). The lifetime maximum cumulative dose of doxorubicin allowed is 500 mg/m^2. There is no maximum dose/exposure for lenvatinib or paclitaxel. The maximum dose for paclitaxel is determined by site's standard of care.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the Informed Consent Form (ICF). The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, Good Clinical

Practice (GCP) and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5. Study Population

Female participants at least 18 years of age with advanced EC will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Type of Participant and Disease Characteristics

- Histologically confirmed diagnosis of endometrial carcinoma.
- Documented evidence of advanced, recurrent or metastatic EC.
- Radiographic evidence of disease progression after 1 prior systemic, platinum-based chemotherapy regimen for EC. Participants may have received up to 1 additional line of platinum-based chemotherapy if given in the neoadjuvant or adjuvant treatment setting.

  Note: There is no restriction regarding prior hormonal therapy.
- Available historical or fresh tumor biopsy specimen for determination of MMR status.
- At least 1 measurable target lesion according to RECIST 1.1 and confirmed by BICR, including the following criteria:
  - Non-nodal lesion that measures ≥1.0 cm in the longest diameter
  - Lymph node (LN) lesion that measures as ≥1.5 cm in the short axis
  - The lesion is suitable for repeat measurement using computed tomography/magnetic resonance imaging (CT/MRI). Lesions that have had external beam radiotherapy (EBRT) or locoregional therapy must show radiographic evidence of subsequent growth.

Demographics

- ECOG performance status of 0 or 1 within 7 days of starting study treatment.
- Female participants age ≥18 years and considered an adult per local regulations at the time of informed consent.

Female participants:

- A female participant is eligible to participate if she is not pregnant (see Appendix 2), not breastfeeding, and at least one of the following conditions applies:
  a.) Not a WOCBP as defined in Appendix 2
  OR
  b.) A WOCBP who agrees to follow the contraceptive guidance in Appendix 2 during the treatment period and for at least 120 days (for participants treated with lenvatinib plus pembrolizumab) or at least 180 days (for participants treated with TPC) after the last dose of study treatment.

Informed Consent

- The participant provides written informed consent for the study.

Additional Criteria

- Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP ≤150/90 mm Hg at Screening and no change in antihypertensive medications within 1 week before C1D1.
- Have adequate organ function as defined in Table 1. Specimens must be collected within 7 days prior to the start of study treatment.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[1]
Renal	
Creatinine OR Measured or calculated[2] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN except for unconjugated hyperbilirubinemia of Gilbert's syndrome.
AST (SGOT), ALT (SGPT), and ALP	≤3 × ULN (≤5 × ULN for participants with liver metastases)[3]
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT)[4]	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

Abbreviations: ALP = alkaline phosphatase; ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCl = creatinine clearance; GFR = glomerular filtration rate; ULN = upper limit of normal.

1. Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within 2 weeks of randomization.
2. Creatinine clearance (CrCl) should be calculated per institutional standard.
3. Participants with ALP values >3 times the ULN and known to have bone metastases can be included.
4. PTT may be performed if local lab is unable to perform aPTT.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Carcinosarcoma (malignant mixed Műllerian tumor), endometrial leiomyosarcoma and endometrial stromal sarcomas.
2. Participants with CNS metastases are not eligible, unless they have completed local therapy (eg, whole brain radiation therapy [WBRT], surgery or radiosurgery) and have discontinued the use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study. Any signs (eg, radiologic) or symptoms of CNS metastases must be stable for at least 4 weeks before starting study treatment.

3. Active malignancy (except for endometrial cancer, definitively treated in-situ carcinomas [e.g. breast, cervix, bladder], or basal or squamous cell carcinoma of the skin) within the past 24 months.
4. Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib.
5. Has a pre-existing Grade ≥3 gastrointestinal or non-gastrointestinal fistula.
6. Radiographic evidence of major blood vessel invasion/infiltration. The degree of tumor invasion/infiltration of major blood vessels should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis following lenvatinib therapy.
7. Clinically significant hemoptysis or tumor bleeding within 2 weeks prior to the first dose of study drug.
8. Significant cardiovascular impairment within 12 months of the first dose of study drug: such as history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction or cerebrovascular accident (CVA) stroke, or cardiac arrhythmia associated with hemodynamic instability.
9. Active infection (any infection requiring systemic treatment).
10. Participants who have not recovered adequately from any toxicity and/or complications from major surgery prior to starting therapy.
11. Participants known to be positive for Human Immunodeficiency Virus (HIV). No HIV testing is required unless mandated by local health authority. Refer to Appendix 9 for country-specific requirements.
12. Known active Hepatitis B (eg, HBsAg reactive) or Hepatitis C (eg, HCV RNA [qualitative] is detected). No testing for hepatitis B or C is required unless mandated by local health authority. Refer to Appendix 9 for country-specific requirements.
13. Has a history of (noninfectious) pneumonitis that required treatment with steroids, or has current pneumonitis.
14. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
15. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.

16. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.
17. Active autoimmune disease (with the exception of psoriasis) that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
18. Has had an allogenic tissue/solid organ transplant.
19. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [β-hCG] (or hCG) test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG [or hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

Prior/Concomitant Therapy

20. Greater than 1 prior systemic chemotherapy regimen (other than adjuvant or neoadjuvant) for EC. Participants may receive up to 2 regimens of platinum-based chemotherapy in total, as long as one is given in the neoadjuvant or adjuvant treatment setting.
21. Prior anticancer treatment within 28 days (or 5 times the half-life time, whichever is shorter). All acute toxicities related to prior treatments must be resolved to Grade ≤1, except for alopecia and Grade ≤2 peripheral neuropathy.
22. Prior treatment with any treatment targeting VEGF-directed angiogenesis, any anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
23. Participants who received prior treatment with an agent directed to a stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX 40, CD137) other than an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, and who discontinued from that treatment due to a Grade 3 or higher immune-related adverse event (irAE).
24. Prior radiation therapy within 21 days prior to start of study treatment with the exception of palliative radiotherapy to bone lesions, which is allowed if completed 2 weeks prior to study treatment start. Participants must have recovered from all radiation-related toxicities and/or complications prior to randomization.
25. Received a live vaccine within 30 days of planned start of study treatment (C1D1). Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

26. Known intolerance to study treatment (or any of the excipients).

Prior/Concurrent Clinical Study Experience

27. Prior enrollment on a clinical study evaluating pembrolizumab and lenvatinib for endometrial carcinoma, regardless of treatment received.
28. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study treatment.

    Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

Diagnostic Assessments

29. Participants with proteinuria >1+ on urine dipstick testing will undergo 24-h urine collection for quantitative assessment of proteinuria. Participants with urine protein ≥1 g/24 h will be ineligible.
30. Prolongation of QTc interval to >480 ms.
31. Left ventricular ejection fraction (LVEF) below the institutional (or local laboratory) normal range as determined by multigated acquisition scan (MUGA) or echocardiogram (ECHO).

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

5.3.2 Contraception

Lenvatinib and pembrolizumab may have adverse effects on a fetus in utero. Refer to Appendix 2 for approved methods of contraception. Refer to the respective IB for detailed information on pembrolizumab and lenvatinib.

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, participants of childbearing potential must adhere to the contraception requirement (Appendix 2) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days (for participants treated with lenvatinib plus pembrolizumab) or up to 180 days (for participants treated with TPC) after the last dose of study medication. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

5.3.3 Pregnancy

If a participant inadvertently becomes pregnant while on study treatment, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to MSD without delay and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to MSD as described in Section 8.4.1.

5.3.4 Use in Nursing Women

It is unknown whether the study treatments are excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breastfeeding are not eligible for enrollment.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any adverse events (AEs) or serious adverse events (SAEs) meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who is discontinued from study treatment will not be replaced.

6. Treatments

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Treatments Administered

The study treatments to be used in this study are outlined below in Table 2 Study Treatment(s).

Table 2 Study Treatment(s)

Study Treatment Name	**Dose Formulation**	**Unit Dose Strength(s)**	**Dosage Level(s)**	**Route of Administration**	**Use**	**Sourcing**
Lenvatinib	Capsule	10 mg, 4 mg[a]	20 mg	Orally QD	Experimental	Central
Pembrolizumab	Solution for infusion	25 mg/mL	200 mg Q3W	IV	Experimental	Central
Doxorubicin	Solution for infusion	Variable	60 mg/m^2 Q3W	IV	Comparator	Local or Central[b]
Paclitaxel	Solution for infusion	Variable	80 mg/m^2 QW[c]	IV	Comparator	Local or Central[b]

Abbreviations: IV = intravenous; Q3W = every 3 weeks; QD = once daily; QW = every week.

a. 4 mg capsules provided for successive dose reduction of lenvatinib, if needed, as described in Section 6.6.1.
b. Provided centrally by the Sponsor except in specific countries where commercial product may be sourced locally.
c. 28-day cycle with weekly administration; 3 weeks on and 1 week off.

All supplies indicated in Table 2 will be provided per the 'Sourcing' row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study etc.).

Refer to Section 8.1.8 for details regarding administration of the study treatment.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of pembrolizumab are provided in the Pharmacy manual. Doxorubicin and paclitaxel should be prepared as outlined in the respective approved labeling or Institutional guidelines. Lenvatinib is a capsule for oral administration and does not require preparation.

6.2.2 Handling, Storage and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country MSD personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by MSD.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of study treatments in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Method of Treatment Assignment

Treatment allocation/randomization will occur centrally using an interactive response technology (IRT) system. There are 2 study treatment arms. Participants will be assigned

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

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.

However, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines, and are not allowed.

For participants in the lenvatinib plus pembrolizumab arm, systemic glucocorticoids are permitted only for the following purposes:

- To modulate symptoms of an AE that is suspected to have an immunologic etiology
- As needed for the prevention of emesis
- Premedication for IV contrast allergies
- Short-term oral or IV use in doses >10mg/day prednisone equivalent for COPD exacerbations
- For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent

In addition, the following glucocorticoid use is allowed:

- For topical use or ocular use
- Intraarticular joint use
- For inhalation in the management of asthma or chronic obstructive pulmonary disease

For participants who, in an assessment by the investigator, require the use of any of the aforementioned treatments for clinical management, continuation of the study medication and further participation in the study must be discussed and agreed upon with MSD.

If participants receive additional anticancer therapies, this will be judged to represent evidence of disease progression, and study medication will be discontinued. These participants should complete all end of treatment assessments and continue to be followed for survival in the Follow-Up Period.

For further information on the prohibited concomitant therapies for doxorubicin or paclitaxel, please refer to their respective Prescribing Information.

6.5.3 Drug-Drug Interactions

There are no drug-drug interaction (DDI)-related concomitant medication prohibitions or restrictions.

Lenvatinib is not expected to clinically meaningfully alter exposure to CYP3A4/ P-glycoprotein (P-gp) substrates based on results from a lenvatinib DDI study with midazolam (a sensitive CYP3A and P-gp substrate).

Clinical studies also showed that co-administration of lenvatinib with either inducers or inhibitors of CYP3A4/P-gp are not of clinical concern.

No drug interaction is expected between pembrolizumab and lenvatinib because of their divergent metabolic pathways. Pembrolizumab is a monoclonal antibody and is primarily catabolized like other proteins, while lenvatinib is metabolized by enzymatic (CYP3A and aldehyde oxidase) and non-enzymatic processes (lenvatinib IB).

6.5.4 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Table 4. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab and/or lenvatinib.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 4 in Section 6.6.2.1 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

6.5.5 Hematopoietic Growth Factors

Primary prophylactic use of granulocyte colony stimulating factors (G-CSF) may be used per the discretion of the treating physician and in line with local guidelines.

6.6 Dose Modification (Escalation/Titration/Other)

Adverse events will be graded using NCI CTCAE Version 4.03. Investigators will decide the probability of the event being related to one or both drugs as to whether dose modification of one or both drugs is required.

Participants who interrupt or discontinue one drug in the pembrolizumab-lenvatinib combination due to toxicity can continue with the other drug in the combination until criteria for treatment discontinuation are met (eg, unacceptable toxicity, disease progression).

Refer to Section 6.6.3 for dose modification guidance for overlapping toxicity for the lenvatinib plus pembrolizumab combination.

6.6.1 Lenvatinib

Lenvatinib dose reduction and interruption for participants who experience lenvatinib-pembrolizumab combination therapy-related toxicity will be in accordance with the dose modification guidelines described in Table 3. An interruption of study treatment for more than 28 days will require MSD approval before treatment can be resumed.

The starting dose of lenvatinib is 20 mg/day for participants enrolled in Arm A. Dose reductions of lenvatinib occur in succession based on the previous dose level (14, 10, and 8 mg/day). Any dose reduction below 8 mg/day must be discussed with MSD. Once the lenvatinib dose has been reduced, it may not be increased at a later date, unless the dose has been mistakenly decreased; in this situation, MSD's approval is required to increase the dose.

Refer to the subsections below for management of hypertension (Section 6.6.1.1), proteinuria (Section 6.6.1.2), diarrhea (Section 6.6.1.3), hepatotoxicity (Section 6.6.1.4), thromboembolic events (Section 6.6.1.5), posterior reversible encephalopathy syndrome/ reversible posterior leukoencephalopathy syndrome (PRES/RPLS; Section 6.6.1.6), hypocalcemia (Section 6.6.1.7), and hemorrhage (Section 6.6.1.8), and gastrointestinal perforation or fistula formation (Section 6.6.1.9), as appropriate, before consulting the dose modification table (Table 3). For overlapping toxicities of pembrolizumab and lenvatinib, please refer to Section 6.6.3.

Table 3 Dose Modification Guidelines for Lenvatinib-Related Adverse Events (for the Lenvatinib-Pembrolizumab Combination Arm)

Treatment-Related Toxicity[a,b]	**Management**	**Dose Adjustment**
Grade 1 or Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c, d] **or Grade 3**[e]		
First occurrence	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 14 mg once a day (1-level reduction)
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 10 mg once a day (1-level reduction)
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 8 mg orally once a day (1-level reduction)
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib	Discuss with MSD
Grade 4[f]**:** Discontinue Study Treatment		

Abbreviations: AE = adverse event; BMI = body mass index; CTCAE = Common Terminology Criteria for Adverse Events; MSD = Merck Sharp & Dohme, Corp.
Note: For grading see CTCAE version 4.03. Collect all AE grades (ie, decreasing and increasing CTCAE grade).

a. An interruption of study treatment for more than 28 days will require MSD's approval before treatment can be resumed.
b. Initiate optimal medical management for nausea, vomiting, hypertension, hypothyroidism and/or diarrhea prior to any lenvatinib interruption or dose reduction.
c. Applicable only to Grade 2 toxicities judged by the participant and/or physician to be intolerable.
d. Obese participants (BMI ≥30) with weight loss do not need to return to the baseline weight or 10% of baseline weight (ie, Grade 1weight loss). These participants may restart the study drug(s) at a lower dose once their weight remains stable for at least 1 week and they have a minimum BMI of 25. The new stable weight should be used as the new baseline for further dose reductions.
e. For asymptomatic laboratory abnormalities, such as Grade ≥3 elevations of amylase and lipase that are not considered clinically relevant by the investigator, continuation of treatment without dose modification should be discussed with MSD.
f. Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

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:

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

- A subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level
- When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is ≥2+.

3. A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when UPCR is ≥2.4.

Grading of Proteinuria

- Grading according to NCI CTCAE v4.03 will be based on the 24-hour urinary protein result if one has been obtained.

Management of Proteinuria

- Management of lenvatinib administration will be based on the grade of proteinuria according to Table 3.
- In the event of nephrotic syndrome, lenvatinib must be discontinued.

Monitoring

- 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.
- Proteinuria monitoring can be performed at the local laboratory or investigator site, but must be managed by the site physician.

6.6.1.3 Management of Diarrhea

An anti-diarrheal agent should be recommended to the participant at the start of study treatment and participants should be instructed and educated to initiate anti-diarrheal treatment at the first onset of soft bowel movements. The choice of anti-diarrheal agent should be individualized to the participant's clinical circumstances and follow standard medical practice. If signs/symptoms of diarrhea persist despite optimal medical management, instructions contained in Table 3 should be followed.

6.6.1.4 Management of Hepatotoxicity

Liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) should be conducted as detailed in the SoA (Section 1.3.1 and Section 1.3.2) and as clinically indicated. If signs/symptoms indicating liver injury occur, instructions contained in Table 3 should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs the study drug must be discontinued.

6.6.1.5 Management of Thromboembolic Events

Participants should be advised to pay attention to symptoms suggestive of venous thromboembolic events which include acute onset of shortness of breath, dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, DVT signs including lower-extremity swelling, and warmth to touch or tenderness. In case any of these symptoms appear,

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.

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.

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab monotherapy, coformulations or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab monotherapy, coformulations or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Recurrent Grade 2 or Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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]		

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).

6.6.2.2 Dose Modification and Toxicity Management of Infusion-reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 5.

Table 5 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: - IV fluids - Antihistamines - NSAIDs - Acetaminophen - Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5 h (± 30 minutes) prior to infusion of pembrolizumab with: • Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 **Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; NSAIDs = nonsteroidal anti-inflammatory drugs; PO = by mouth.
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.
For further information, please refer to the CTCAE v4.03 at http://ctep.cancer.gov

6.6.3 Dose Modifications for Overlapping Toxicities

Based on the known toxicity profiles of pembrolizumab and lenvatinib, certain treatment-related AEs are uniquely associated with one drug versus the other. For example, hypertension, arterial thrombotic events, proteinuria, and hemorrhagic events are known risks for lenvatinib treatment, while immune-related AEs are risks for pembrolizumab treatment. However, certain AEs, such as such as diarrhea, hypothyroidism, and liver enzyme elevation, may be initially considered attributable to either study drug. Therefore, evaluation of attribution is important for determining the study drug most likely related to the AE, or an alternative etiology, and subsequently proper clinical management. The following aspects should be considered:

1. Timing of AE onset

   Since lenvatinib is dosed daily and continuously due to a relatively short half-life (28 hours), and pembrolizumab is dosed Q3W due to a long half-life, lenvatinib can be interrupted to assess whether an AE improves/resolves with dechallenge (ie, interruption of treatment) based on the following 2 scenarios:

   - If an AE is identified during a treatment cycle (ie, between 2 pembrolizumab doses), only lenvatinib dose interruption is needed.
   - If an AE is identified at the beginning of a treatment cycle, lenvatinib can be interrupted and dosing of pembrolizumab should be held.

   If the participant recovers from an AE in response to lenvatinib interruption (ie, positive dechallenge), the event is more likely to be related to lenvatinib. Otherwise, after excluding other alternative explanations, an immune-related AE should be considered.

2. Severity of AE

   If an AE is suspected to be treatment-related and is severe/life-threatening at the time of onset or is rapidly worsened, action including interrupting both drugs and initiating treatment with a corticosteroid (with exception of hypothyroidism, TIDM) and other supportive care should be taken promptly.

3. Participants receiving the combination therapy (pembrolizumab plus lenvatinib) must discontinue study intervention if any of the following occur:

   1) ALT or AST >5 × ULN for more than 2 weeks.

      Pembrolizumab will have already been permanently discontinued per Table 4, but lenvatinib may be administered at a reduced dose by the time this criterion is met and must be permanently discontinued immediately.

   2) ALT or AST >3 × ULN and (TBL >2 × ULN or INR >1.5).

      Although Table 4 advises pembrolizumab to be withheld (interrupted), and Table 3 advises lenvatinib to have no dose modification or a reduction, if this criterion is met, both drugs must be permanently discontinued immediately.

6.6.4 Other Allowed Dose Interruptions for Lenvatinib and Pembrolizumab

If the participant is receiving treatment with lenvatinib and requires surgery during the study, the stop time and restart time of lenvatinib should be as follows:

- For minor procedures: stop lenvatinib at least 2 days before the procedure and restart it at least 2 days after, once there is evidence of adequate healing and no risk of bleeding.
- For major procedures: stop lenvatinib at least 1 week (5 half-lives) prior to surgery and then restart it at least 1 week after, once there is evidence of adequate healing and no risk of bleeding.

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical/surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with MSD. The reason for interruption should be documented in the participant's study record.

6.6.5 Second Course Phase (Retreatment Period)

All participants who stop treatment with lenvatinib plus pembrolizumab with SD or better may be eligible for up to an additional year of treatment with pembrolizumab (17 cycles) ± lenvatinib if they progress after stopping study treatment from the initial treatment period. If lenvatinib is stopped due to toxicity during the initial treatment period, only pembrolizumab will be administered during second course, otherwise lenvatinib may be administered with pembrolizumab during second course. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the participant meets the following conditions:

Either

- Stopped initial treatment with pembrolizumab +/- stopping lenvatinib after attaining an investigator-determined confirmed CR according to RECIST 1.1
  - Was treated for at least 8 cycles with l pembrolizumab +/- lenvatinib before discontinuing therapy
  - Received at least 2 treatment cycles of pembrolizumab +/- lenvatinib beyond the date when the initial CR was declared

OR

- Had SD, PR or CR and stopped pembrolizumab +/- stopping lenvatinib treatment after completion of 35 administrations (approximately 2 years) of study treatment for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined radiographic disease progression by RECIST 1.1 after stopping initial treatment with pembrolizumab, and
- No new anticancer treatment was administered after the last dose of study treatment, and

- The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
- The study is ongoing

An objective response or disease progression that occurs during the Second Course Phase for a participant will not be counted as an event for the primary analysis of either endpoint in this study.

Note: Participants in the crossover phase are not eligible for the Second Course Phase.

Visit requirements for the Second Course Phase are outlined in Section 1.3.2.

6.6.6 Treatment of Physician's Choice

Management for participants who experience doxorubicin-related or paclitaxel-related toxicity will be in accordance with the respective doxorubicin or paclitaxel prescribing information in each country/region or local institutional guidelines.

6.7 Treatment After the End of the Study

There is no study-specified treatment following the end of the study.

6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study site personnel, the Sponsor, MSD and/or designee are not blinded. Study treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

7. Discontinuation of Study Treatment and Participant Withdrawal

7.1 Discontinuation of Study Treatment

Discontinuation of study treatment does not represent withdrawal from the study.

As certain data on clinical events beyond study treatment discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study treatment. Therefore, all participants who discontinue study treatment prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.12.3.

Participants may discontinue study treatment at any time for any reason or be discontinued from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or MSD if study treatment is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 8.1.9.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study treatment.

- Radiographic disease progression documented per RECIST 1.1 by BICR, and when clinically appropriate, confirmed by the site per iRECIST (Section 8.2.1.6).

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- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Noncompliance with study treatment or procedure requirements
- Any study treatment-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6
- Unacceptable adverse event(s)
- Completion of 35 treatments (approximately 2 years) with pembrolizumab or a lifetime cumulative dose of 500 mg/m^2 of doxorubicin.

  Note: Participants in Arm A will continue on lenvatinib alone until disease progression is confirmed by BICR, development of unacceptable toxicity, or withdrawal of consent (see Section 4.1.2).

  Note: The number of treatments is calculated starting with the first dose of pembrolizumab.
- The participant has a confirmed positive serum/urine pregnancy test.
- ALT or AST elevation meeting the following criteria:
  - ALT or AST >5 × ULN for more than 2 weeks
    Pembrolizumab will have already been permanently discontinued per Table 4, but lenvatinib may be administered at a reduced dose by the time this criterion is met and must be permanently discontinued immediately.
  - ALT or AST >3 × ULN and (TBL >2 × ULN or INR > 1.5)
    Although Table 4 advises pembrolizumab to be withheld (interrupted), and Table 3 advises lenvatinib to have no dose modification or a reduction, if this criterion is met, both drugs must be permanently discontinued immediately.
  - If a participant with liver metastasis has Grade 2 AST or ALT at the start of study treatment, and the AST or ALT value increases by ⩾50% relative to baseline and lasts for ⩾1 week, then the participant should permanently discontinue study intervention.

For participants who are discontinued from study treatment but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

7.1.1 Discontinuation of Pembrolizumab After Complete Response

Discontinuation of pembrolizumab may be considered for participants who have attained a confirmed CR that have been treated for at least 8 cycles (at least 24 weeks) with lenvatinib plus pembrolizumab and had at least 2 treatments with lenvatinib plus pembrolizumab beyond the date when the initial CR was declared. Participants who then experience radiographic disease progression may be eligible for up to 1 year of additional treatment with

lenvatinib plus pembrolizumab at the discretion of the investigator as detailed in Section 6.6.5.

Participants will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 6.6.5. Response or progression in this Second Course Phase will not count towards the ORR and PFS of the primary endpoint in this study.

7.1.2 Crossover Phase

Participants who were randomized to Arm B (TPC) and experience investigator-defined disease progression per RECIST 1.1, while in the study treatment phase or after stopping treatment on study but remaining in Efficacy Follow-up or Survival Follow-up, and have not yet started subsequent anticancer therapy, or withdrawn consent (from either study treatment or follow-up phases), may be eligible for the Crossover Phase. Prior to entering the Crossover Phase, provided the study is still ongoing, participants should meet all eligibility criteria, with the exception of exclusion criteria #20, #21, #24 and #28 (refer to Sections 5.1 and 5.2).

Participants may be eligible for up to two years (35 cycles) of treatment with lenvatinib plus pembrolizumab. A Second Course Phase will not be made available for participants in the Crossover Phase. Participants who complete the Crossover phase will enter the Post-Crossover Phase. Additional details are provided in Section 1.3.3. Response or progression in the Crossover Phase will not count towards the ORR and PFS of the primary endpoint in this study.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for assuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or MSD for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

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).

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.

Study Treatment should begin within 3 days of randomization.

8.1.8.1 Timing of Dose Administration

8.1.8.1.1 Lenvatinib

Lenvatinib 20 mg (two 10-mg capsules) once daily will be taken orally with water (with or without food) at approximately the same time each day in each 21-day cycle. However, on Day 1 of Cycles 1 and 2, lenvatinib will be administered 0 to 4 hours after completion of pembrolizumab administration.

If a lenvatinib dose is missed and cannot be taken within 12 hours then that dose should be skipped, and the next dose should be taken at the usual time of administration.

8.1.8.1.2 Pembrolizumab

Pembrolizumab will be administered as a 30-minute IV infusion on Day 1 of each 21-day cycle. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of –5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes: –5 min/+10 min).

After Cycle 1 Day 1, pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each subsequent cycle due to administrative reasons.

8.1.8.1.3 Treatment of Physician's Choice

TPC consists of either doxorubicin hydrochloride or paclitaxel. Doxorubicin hydrochloride will be administered by IV bolus or 1-hour infusion (or per institutional guidelines) at a dose of 60 mg/m^2 on Day 1 of each 21-day cycle.

Paclitaxel will be administered IV at a dose of 80 mg/m^2 administered as a 1-hour IV infusion (or per institutional guidelines on Days 1, 8, and 15 of each 28-day cycle; i.e. 3 weeks on, 1 week off). The administration procedure should follow the approved prescribing information for doxorubicin or paclitaxel in each country/region or institutional guidelines.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study treatment prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits.

When a participant withdraws from participation in the study, all applicable activities scheduled for the discontinuation visit (End of Treatment visit) should be performed (at the time of withdrawal). Any AEs which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4 .

If discontinuation occurs ≥30 days after the last dose of study treatment, a Safety Follow-up Visit (Section 8.12.3.1) is not required. In this situation, all procedures required at both the EOT visit and the safety follow-up visit should be performed.

8.1.10 Participant Blinding/Unblinding

This is an open label study; there is no blinding for this study.

8.1.11 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.1.12 Demography

Participant demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity.

8.2 Efficacy/Immunogenicity Assessments

8.2.1 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the CIV can be found in the Site Imaging Manual (SIM). Tumor imaging of the chest is to be acquired by computed tomography (CT). For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) is the preferred modality; however, CT with iodinated contrast may be used when contrast-enhanced MRI is contraindicated, or when mandated by local practice. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging. Note: for the purposes of assessing tumor imaging, the term “Investigator” refers to the local investigator at the site and/or the radiological reviewer located at the site or at an offsite facility.

Participant eligibility will be determined using prospective BICR assessment based on RECIST 1.1. All scheduled images for all study participants from the sites will be submitted to the CIV. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but which demonstrate radiologic progression, should also be submitted to the CIV.

When the Investigator identifies radiographic progression per RECIST 1.1, the CIV will perform expedited verification of radiologic PD and communicate the results to the study site and MSD (See Section 8.2.1.5 and Figure 2). Treatment should continue until PD has been verified. All decisions to continue treatment beyond 2 consecutive scans showing progression at least 4 weeks apart must be discussed with the MSD Medical Monitor (Section 8.2.1.6 and Appendix 5). CCI [redacted] Images should continue to be submitted to the CIV.

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.

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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.

8.2.1.4 Second Course (Retreatment) Tumor Imaging

Tumor imaging must be performed within 28 days prior to restarting treatment with pembrolizumab ± lenvatinib. Local reading (Investigator assessment with site radiology reading) will be used to determine eligibility. All second course imaging should be submitted to the CIV for quality control, storage, and possible retrospective review.

The first on study imaging assessment should be performed at 12 weeks (84 days ±7 days) after the restart of treatment. Subsequent tumor imaging should be performed every 12 weeks (84 days ±7 days) or more frequently, if clinically indicated.

CCI [redacted]

Imaging should continue to be performed until disease progression, the start of a new anticancer treatment, withdrawal of consent, death, or notification by MSD, whichever occurs first. CCI [redacted]

For participants who discontinue Second Course 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. For participants who discontinue study treatment due to documented disease progression, this is the final required tumor imaging.

For participants who discontinue Second Course study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 12 weeks (84 days ±7 days) or as clinically indicated thereafter until either the start of a new anticancer treatment, disease progression, death, withdrawal of consent, or the end of the study, whichever occurs first.

8.2.1.4.1 Bone Imaging During Second Course

A bone scan (^{99}m-technetium-based scintigraphy, whole body bone MRI, or NaF PET) prior to restarting pembrolizumab ± lenvatinib will only be performed in participants who have a history of bone metastases or are clinically symptomatic. The bone scan prior to restarting treatment is only required if the previous scan was not performed within the prior 6 weeks. Subsequent bone scans in these participants will be performed every 24 weeks (±7 days) after restarting pembrolizumab ± lenvatinib, or as clinically indicated.

8.2.1.4.2 Brain Imaging During Second Course

A brain scan (CT of the brain with contrast or MRI of the brain pre- and post-gadolinium) within 28 days of restarting pembrolizumab ± lenvatinib 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 restarting pembrolizumab ± lenvatinib.

8.2.1.5 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used by BICR as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study treatment). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden. Initial tumor imaging showing site-assessed PD should be submitted immediately for BICR verification of PD. The site will be notified if the BICR verifies PD using RECIST 1.1. Figure 2 illustrates the imaging flow involving verification of PD for clinically stable participants.

8.2.1.6 CCI

CCI

CCI [redacted]

[redacted]

CCI [redacted]

CCI [redacted]

8.2.2 Health-Related Quality of Life Assessments

HRQoL will be assessed at Cycle 1 Day 1 (prior to first dose of study drug), on Day 1 of each subsequent cycle, and at time of discontinuation (End of Treatment visit). Participants will be asked to complete the HRQoL questionnaires for the equivalent of 4 cycle lengths (ie, either every 21 or 28 days depending on assigned treatment) following the End of Treatment visit. Completion of the HRQoL questionnaires following the End of Treatment visit is not mandatory; however, every effort should be made to collect this information. Following the End of Treatment visit, the HRQoL questionnaires will be completed via the Web Diary from the participants' personal electronic device. At the time of the End of Treatment visit, participants should be invited to register for the Web Diary to ensure they receive reminders when the questionnaires are due for completion. Detailed instructions can be found in the CRF Health Site Manual.

Every effort should be made to administer HRQoL surveys prior to study drug administration and before other assessments and procedures. Participants will complete the questionnaires in the following order: CCI [redacted] 2) EORTC QLQ-C30, then 3) CCI [redacted]

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

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.

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.

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

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.

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

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.

c. For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to the first dose of study treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

d. Centrally assessed MMR status must be available prior to randomization. If MMR result is unavailable within 28 days from when original consent was obtained, an exception may be granted after consultation with MSD.

Upon consultation with the MSD Medical Monitor, participants may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria is met. Participants who are rescreened will retain their original screening number.

8.12.2 Treatment Period

Visit requirements are outlined in the SoA (Section 1.3.1, Section 1.3.2, and Section 1.3.3). Assessments/procedures are to be performed prior to the administration of study treatment.

8.12.2.1 Crossover Phase

Participants on the TPC arm (as initial treatment) who develop investigator-assessed disease progression per RECIST 1.1 and stop receiving the investigator's treatment of choice, doxorubicin or paclitaxel, may enter the Crossover Phase to receive lenvatinib plus pembrolizumab, if all eligibility criteria are met. These participants were initially randomized to the TPC arm, taken at least one dose and subsequently discontinued treatment with doxorubicin or paclitaxel.

Participants who initiate a new anticancer therapy or withdraw consent (from either study treatment, Efficacy Follow-up, or Survival Follow-up) are not eligible for crossover.

Participants will have laboratory assessments while receiving study treatment as outlined in the Crossover Schedule of Activities in Section 1.3.3.

The Crossover Phase of the study is only available if the study remains open and the participant meets all the required eligibility criteria, except exclusions #20, #21, #24 and #28. Inclusion and exclusion criteria are defined in Sections 5.1 and 5.2.

Visit requirements are outlined in Section 1.3.3 – SoA.

8.12.3 Post-treatment Visit

8.12.3.1 Safety Follow-up

The mandatory safety follow-up visit should be conducted approximately 30 days after the last dose of study treatment or before the initiation of a new anticancer treatment, whichever comes first.

All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Participants with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anticancer therapy, whichever occurs first. Serious AEs that occur within

120 days of the end of treatment or before initiation of a new anticancer treatment should also be followed and recorded.

Participants who are eligible for retreatment with pembrolizumab may have up to 2 safety follow-up visits, 1 after the Initial Treatment Period and 1 after the Second Course Treatment.

Participants in the TPC arm who are eligible for treatment with lenvatinib plus pembrolizumab in the Crossover Phase (as described in Section 8.12.2.1) may have up to two safety follow-up visits, one after the initial Treatment Period and one after the Crossover Phase.

8.12.3.2 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study treatment or who discontinue study treatment for a reason other than disease progression will move into the Efficacy Follow-Up Phase and should be assessed approximately every 8 weeks (or more frequently as needed) by clinic visit to monitor disease status; if a clinic visit is not feasible, the participant may be contacted by telephone or e-mail. The Sponsor may request survival status to be assessed at additional time points during the course of the study (not to exceed approximately 12 weeks). Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, end of study or if the participant begins retreatment with pembrolizumab as detailed in Section 6.6.5. Information regarding post-study anticancer treatment will be collected if new treatment is initiated. Participants will also be asked to complete HRQoL questionnaires as outlined in Section 8.2.2. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter the Survival Follow-up Phase.

All participants who discontinue study drug treatment prior to disease progression will continue to undergo tumor assessments every 8 weeks in the Follow-up Period until disease progression is documented and confirmed by BICR or a new anticancer therapy is initiated, unless the participant withdraws consent. Following the primary analysis for the study, tumor assessments should be performed every 12 weeks or more frequently per local standard of care.

Participants who are eligible for retreatment with pembrolizumab according to the criteria in Section 6.6.5 will move from the Efficacy Follow-Up Phase to the Second Course Phase when they experience disease progression. Details are provided in the SoA (Section 1.3.2) for retreatment with pembrolizumab.

Participants in the TPC arm who have discontinued study treatment and opt to receive treatment with lenvatinib plus pembrolizumab in the Crossover Phase (according to the criteria in Section 8.12.2.1) may move from the Efficacy Follow-up Phase to the Crossover Phase, if they experience investigator-defined disease progression by RECIST 1.1. Details are provided in Section 1.3.3 – Crossover Phase for TPC Arm Only.

8.12.3.3 Survival Follow-up Contact

Participant survival follow-up status will be assessed approximately every 12 weeks until death, withdrawal of consent, or the end of the study, whichever occurs first.

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.

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.

Interim Analyses	Two interim analyses are planned in this study and will be performed by an independent unblinded statistician and programmer. Results of these analyses will be reviewed by the DMC. Details are provided in Section 9.7.
	• Interim Analysis 1 (IA1)
	  ○ Timing: to be performed after both ~368 OS events have been observed in the pMMR participants and at least 6 months after last participant randomized
	  ○ Primary purpose: final efficacy analysis for PFS and interim efficacy analysis for OS
	• Interim Analysis 2 (IA2)
	  ○ Timing: to be performed after both ~463 OS events have been observed in the pMMR participants and at least 12 months after last participant randomized
	  ○ Primary purpose: interim efficacy analysis for OS
	• Final Analysis (FA)
	  ○ Timing: to be performed after both ~526 OS events have been observed in the pMMR participants and at least 18 months after last participant randomized
	  ○ Primary purpose: final efficacy analysis for OS

Multiplicity	The total family-wise error rate (Type I error) among the 2 primary PFS and OS analyses, ORR analysis, and for pMMR and all-comer participants is strongly controlled at one-sided 0.025 level. A 0.0005 Type I error rate is initially allocated to test PFS and 0.0245 Type I error rate is initially allocated to test OS between two treatment arms in pMMR participants. Details of alpha allocation strategy among hypotheses of PFS, OS, and ORR are provided in Section 9.8 Multiplicity. The study will be considered positive if either testing of PFS or testing of OS is significant in pMMR participants.
Sample Size and Power	The planned sample size is approximately 780 participants (660 pMMR participants and 120 dMMR participants) with 330 pMMR participants and 60 dMMR participants in each arm. For the pMMR participants: With approximately 564 PFS events at the planned PFS analysis, the study will have at least 99% of power to detect a hazard ratio of 0.55 at the one-sided 0.0005 significance level. With approximately 368, 463, and 526 OS events in the pMMR participants at the planned IA1, IA2, and final OS analysis (FA), respectively, the study will have 90% power to detect a hazard ratio of 0.75 at the one-sided 0.0245 significance level.

Following Amendment 08, the pre-planned second interim analysis (IA2) is no longer required and will not be performed. This is because the success criteria for the study hypotheses of PFS, OS, and ORR were met at the first interim analysis (IA1).The prespecified final analysis will be performed without multiplicity adjustment after approximately 526 OS events have been observed in the pMMR participants and at least 18 months after the last participant was randomized. Updated analyses may be performed during the trial at any time point to provide additional estimates with longer follow-up.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of MSD.

MSD will generate the randomized allocation schedule(s) for study treatment assignment for this protocol, and the randomization will be implemented in IRT.

Although the study is open label, analyses or summaries generated by randomized treatment assignment, and actual treatment received status will be limited and documented.

The external DMC will serve as the primary reviewer of the unblinded results of the interim analyses and will make recommendations for discontinuation of the study or modification to a Joint Executive Oversight Committee (EOC). Depending on the recommendation of the external DMC, the Sponsor or MSD may prepare a regulatory submission. If the external DMC recommends modifications to the design of the protocol or discontinuation of the study, this EOC and limited additional Sponsor/MSD personnel may be unblinded to results at the treatment level in order to act on these recommendations. Additional logistical details, revisions to the above plan and data monitoring guidance will be provided in the DMC charter.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3 – Objectives/Hypotheses and Endpoints.

9.4 Analysis Endpoints

9.4.1 Primary Endpoints

- PFS by BICR - defined as the time from the date of randomization to the date of the first documentation of disease progression, as determined by blinded BICR of objective radiographic disease progression per RECIST 1.1 or death due to any cause (whichever occurs first). See Section 9.6.1 – Statistical Methods for Efficacy Analyses for definition of censoring.
- OS - defined as the time from the date of randomization to the date of death due to any cause. Participants who are lost to follow-up and those who are alive at the date of data cutoff will be censored at the date the participant was last known alive, or date of data cutoff, whichever occurs first.

9.4.2 Secondary Endpoints

- ORR - defined as the proportion of participants who have best overall response of either CR or PR as determined by BICR per RECIST 1.1.
- HRQoL will be assessed using the global score of the EORTC QLQ-C30.
- Safety will be assessed summarizing the incidence of TEAEs, SAEs, and irAEs; proportion of participants who discontinued treatment due to TEAEs; and 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).
- Plasma concentration of lenvatinib versus time.
- Model-predicted clearance and AUC for lenvatinib.

9.4.3 Exploratory Endpoints

- CCI [redacted]

- 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.

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

assessment. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 based on BICR, 2 sensitivity analyses with a different set of censoring rules will be performed. The first sensitivity analysis handles participants who miss more than 1 disease assessment (with or without a subsequent death or progression) differently from the primary analysis. The second sensitivity analysis handles participants who discontinue treatment or initiate an anticancer treatment subsequent to discontinuation of study-specified treatments differently from the primary analysis. The censoring rules for primary and sensitivity analyses are summarized in Table 8.

If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

Table 8 Censoring Rules for Primary Analysis of Progression-Free Survival Based on RECIST 1.1

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
PD or death documented after ≤1 missed disease assessment, and before new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study or completed study treatment.
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment if new anticancer treatment is initiated; otherwise progressed at treatment discontinuation if treatment is discontinued due to reasons other than complete response; otherwise censored at last disease assessment if still on study therapy or completed the study therapy

Abbreviations: PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumors.

Overall Survival

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival 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). The HR and its 95% CI from the stratified Cox model 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. Participants without documented death at the time of analysis will be censored at the date of last known contact. Restricted Mean Survival Time (RMST) method may be conducted for OS to account for the possible non-proportional hazards effect.

9.6.1.2 Secondary Efficacy Analysis

Objective Response Rate (ORR)

Stratified Miettinen and Nurminen's method will be used for comparison of the ORR between two treatment groups. The difference in ORR and its 95% confidence interval from the stratified Miettinen and Nurminen's method with strata weighting by sample size will be reported. The stratification factors used for randomization (See Section 6.3.1.1) will be applied to the analysis.

9.6.2 Statistical Analysis for Safety Analysis

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, vital signs, and ECG measurements.

The analysis of safety results will follow a tiered approach (Table 9). The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as system organ class terms) and events that meet predefined limits of change (PDLCs) in laboratory values, vital signs and ECG parameters are either prespecified as "Tier 1" endpoints or will be classified as belonging to "Tier 2" or "Tier 3" based on the observed proportions of participants with an event.

Tier 1 Events

Safety parameters that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. AEs of special interest (AEOSIs) that are immune-mediated or potentially immune-mediated are well documented and will be evaluated separately; however, these events have been characterized consistently throughout the pembrolizumab clinical development program and determination of statistical significance is not expected to add value to the safety evaluation. Further, the combination of pembrolizumab and lenvatinib has not been associated with any new safety signals. Additionally, there are no known AEs associated with participants for which determination of a p-value is expected to impact the safety assessment. Therefore, there are no Tier 1 events in this study.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events using the Miettinen and Nurminen method, an unconditional, asymptotic method [Miettinen, O. 1985].

Membership in Tier 2 requires that at least 10% of participants in any treatment group exhibit the event; all other AEs and predefined limits of change will belong to Tier 3. The threshold of at least 10% of participants was chosen for Tier 2 events because the population enrolled in this study is in critical condition and usually experiences various AEs of similar types regardless of treatment; events reported less frequently than 10% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, Grade 3 to 5 AEs (≥5% of participants in 1 of the treatment groups) and SAEs (≥1% of participants in 1 of the treatment groups) will be considered Tier 2 endpoints. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not as a formal method for assessing the statistical significance of the between-group differences.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. The broad AE categories consisting of the proportion of participants with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, a Grade 3-5 AE, a drug-related Grade 3-5 AE, and discontinuation due to an AE will be considered Tier 3 endpoints. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Table 9 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Grade 3-5 AE (incidence ≥5% of participants in one of the treatment groups)		X	X
	Serious AE (incidence ≥1% of participants in one of the treatment groups)		X	X
	AEs (incidence ≥10% of participants in one of the treatment groups)		X	X
Tier 3	Any AE			X
	Any Grade 3-5 AE			X
	Any Serious AE			X
	Any Drug-Related AE			X
	Any Serious and Drug-Related AE			X
	Any Grade 3-5 and Drug-Related AE			X
	Discontinuation due to AE			X
	Death			X
	Specific AEs, SOCs (incidence >0% of participants in all of the treatment groups)			X
	Change from Baseline Results (lab toxicity shift, vital signs)			X
Abbreviations: AE = adverse event; CI = confidence interval; SOC = system organ class.				

9.6.3 Statistical Analysis for Health-Related Quality of Life Data

For HRQoL analyses, summary statistics of the scores for the derived functional/symptom scales according to the scoring manual and global health status scores will be summarized by treatment arm at each time point. A detailed prespecified HRQoL analysis plan following FDA and EMA PRO Guidelines will be described in a separate SAP.

9.6.4 Summaries of Baseline Characteristics and Demographics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened, randomized, and the primary reason for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (eg, age, race, etc.) and baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

The safety monitoring and efficacy interim analyses will be conducted by the external DMC. Minutes from the open meetings of the DMC will be provided if requested by regulatory agencies. The recommendation whether to stop the study will be reached by the DMC based

on their review of data with treatment information. The function and membership of the DMC will be described in the DMC charter.

9.7.1 Safety Interim Analyses

The external DMC will conduct regular safety monitoring. The timing of the safety monitoring will be specified in the DMC charter.

9.7.2 Efficacy Interim Analyses

Two interim analyses are planned in addition to the final analysis for this study. The interim analyses will be performed by an independent unblinded statistician and programmer. Results of these analyses will be reviewed by the external DMC.

The PFS analysis will be performed only at the time of the first interim analysis of the study and this will be the final PFS analysis. OS analyses will be performed at the first interim, second interim, and final analysis. The Lan-DeMets spending function with O'Brien-Fleming boundary will be used for alpha allocation among the interim and final analyses of OS. Details of the boundaries for establishing statistical significance with regard to efficacy are discussed in Section 9.8. The analyses planned, endpoints evaluated, and drivers of timing are summarized in Table 10.

Table 10 Summary of Interim and Final Analysis Strategy for the pMMR Participants

Analyses	Key Endpoints	Timing	Estimated Time after First Participant Randomized	Primary Purpose of Analysis
IA1	PFS OS	Both ~368 OS events and at least 6 months after last participant randomized	~27 months	• Final PFS analysis • Interim OS analysis
IA2	OS	Both ~463 OS events and at least 12 months after last participant randomized	~35 months	• Interim OS analysis
FA	OS	Both ~526 OS events and at least 18 months after last participant randomized †	~43 months †	• Final OS analysis

Abbreviations: FA = final analysis; IA1 = interim analysis 1; IA2 = interim analysis 2; OS = overall survival; PFS = progression-free survival; pMMR = mismatch repair proficient.
† Note that if events accrue slower than expected for the FA, the Sponsor may conduct the analysis up to 3 months after the estimated timing of the FA (ie., ~46 months after first participant randomized).

As described in Section 9.8, the PFS and OS analyses for the all-comer participants will be performed as listed in Table 10 if the respective analyses are successful in the pMMR participants.

Following Amendment 08, the pre-planned IA2 is no longer required and will not be performed; further details are described in Section 9.1.

9.8 Multiplicity

The total family-wise error rate (Type I error) among the 2 primary PFS and OS analyses, ORR analysis, and for pMMR and all-comer participants is strongly controlled at one-sided 0.025 level. The multiplicity strategy will follow the graphical approach of Maurer and Bretz [Maurer, W. 2013]. Figure 3 shows the initial one-sided α-allocation for each hypothesis in the ellipse representing the hypothesis. The initial weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses.

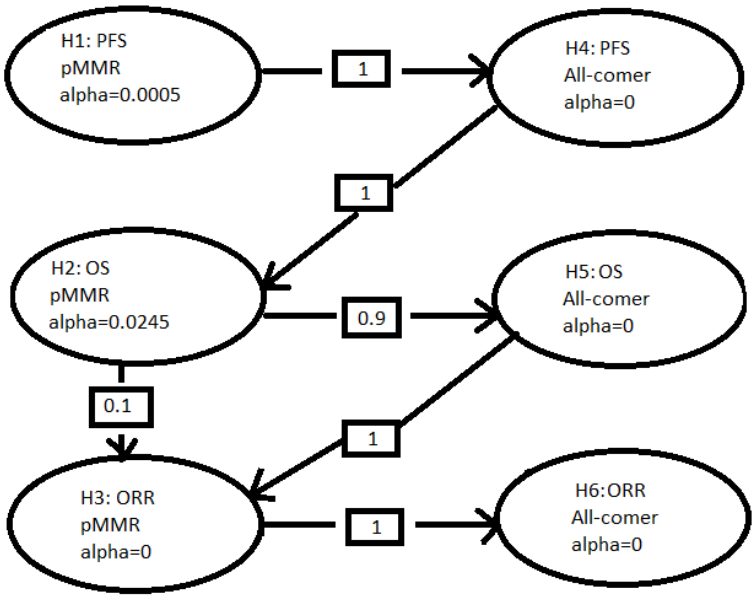


Figure 3 Multiplicity Graph for Type I Error Control of Study Hypotheses

Abbreviations: ORR = objective response rate; OS = overall survival; PFS = progression-free survival; pMMR = mismatch repair proficient.

The study initially allocates α = 0.0005, one-sided, to test PFS for pMMR participants and initially allocates α =0.0245, one-sided to test OS for pMMR participants between the two treatment arms. As shown in Figure 3, if the null hypothesis for PFS for pMMR is rejected, α = 0.0005 will be passed to the test for PFS for all-comer participants. And if the null hypothesis for PFS for all-comer participants is rejected, α = 0.0005 will be passed to the test for OS for pMMR, therefore OS for pMMR will be tested at α =0.025. The study will be considered positive if either testing of PFS or testing of OS is significant in pMMR participants.

Table 11 shows the bounds and boundary properties for OS hypothesis testing derived using a Lan-DeMets spending function approximating O'Brien-Fleming bounds. The bounds provided in the table assume that the expected number of OS events at IA1, IA2, and FA are 368, 463, and 526, respectively. At the time of an analysis, the observed number of events may differ from the expected. To avoid overspending at an interim analysis and leave reasonable alpha for the final analysis, the minimum alpha spending strategy will be adopted. At an IA, the information fraction used in Lan-DeMets spending function to determine the

alpha spending at the IA will be based on the minimum of the expected information fraction and the actual information fraction at each analysis. Specifically:

- In the scenario that the events accrue slower than expected and the observed number of events is less than the expected number of events at a given analysis, the information fraction will be calculated as the observed number of events at the interim analysis over the target number of events at FA.
- In the scenario that the events accrue faster than expected and the observed number of events exceeds the expected number of events at a given analysis, the information fraction will be calculated as the expected number of events at the interim analysis over the target number of events at FA.

The final analysis will use the remaining Type I error that has not been spent at the earlier analyses. The observed event counts for all analyses will be used to compute correlations.

Of note, while the information fraction used for the alpha spending calculation will be the minimum of the actual information fraction and the expected information fraction, the correlations required for deriving the bounds will still be computed using the actual information fraction based on the observed number of events at each analysis over the target number of events at FA.

The minimum spending approach assumes timing is not based on any observed Z-value and thus the Z test statistics used for testing conditioned on timing are multivariate normal. Given the probabilities derived with the proposed spending method, the correlations based on actual event counts are used to compute bounds that control the Type I error at the specified alpha level for a given hypothesis conditioned on the interim analysis timing. Since this is true regardless of what is conditioned on, the overall Type I error for a given hypothesis unconditionally is controlled at the specified level. By using more conservative spending early in the study, power can be retained to detect situations where the treatment effect may be delayed.

Table 11 Boundary Properties for Planned Analyses of OS Based on Potential Alpha-Levels to be Used for Testing in the pMMR Participants

Analysis	Value	α =0.0245	α =0.025
IA1 N: 660 OS events: 368 (70%*) Month: 27	Z	2.448	2.440
	p (1-sided) †	0.0072	0.0073
	HR at bound ‡	0.7747	0.7753
	P(Cross) if HR=1 §	0.0072	0.0073
	P(Cross) if HR=0.75 ǀ	0.6234	0.6259
IA2 N: 660 OS Events: 463 (88%*) Month: 35	Z	2.187	2.178
	p (1-sided) †	0.0144	0.0147
	HR at bound ‡	0.8160	0.8167
	P(Cross) if HR=1 §	0.0165	0.0169
	P(Cross) if HR=0.75 ǀ	0.8260	0.8285
FA N: 660 OS Events: 526 Month: 43	Z	2.069	2.061
	p (1-sided) †	0.0193	0.0196
	HR at bound ‡	0.8348	0.8355
	P(Cross) if HR=1 §	0.0245	0.0250
	P(Cross) if HR=0.75 ǀ	0.9009	0.9025

Abbreviation: HR = hazard ratio; IA= interim analysis; FA= final analysis.
The number of events and timings are estimated.
* Percentage of total planned events at the interim analysis.
† *p* (1-sided) is the nominal α for group sequential testing.
‡ HR at bound is the approximate observed HR required to reach an efficacy bound.
§ P(Cross) if HR=1 is the probability of crossing a bound under the null hypothesis.
ǀ P(Cross) if HR=0.75 is the probability of crossing a bound under the alternative hypothesis.

The study will continue if the interim OS analyses are not statistically significant. If the IA2 or final OS analysis is statistically significant, ORR will be tested at the time of IA2 or final OS analysis using interim data (at IA1) to protect family-wise type I error rate.

Following Amendment 08, the pre-planned IA2 is no longer required and will not be performed; further details are described in Section 9.1.

9.9 Sample Size and Power Calculations

The sample size is estimated based on the primary endpoints PFS and OS. A total of approximately 780 participants (including 660 participants from pMMR and 120 participants from dMMR participants) will be randomized in a 1:1 ratio (approximately 330 participants from pMMR and 60 participants from dMMR participants in each treatment arm).

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.

Sample size and power calculations are based on pMMR participants:

The study is designed to have 90% power to detect a statistically significant difference in OS at one-sided α=0.0245 and as a result, the study will also have at least 99% power to detect a statistical significant difference in PFS at one-sided α=0.0005.

Assuming an accrual period of 19 months and a follow-up period of 24 months, a total of 660 participants are required to observe 526 death events by the time of 43 months after the first participant is randomized (19 months enrollment plus 24 months follow-up period).

For OS, a total of 526 OS events are required to detect a statistically significant difference at 0.0245 level with 90% power, under the following assumptions that: 1) the hazard ratio is 0.75 (median OS is 16.4 months in Arm A and 12.3 months in Arm B), 2) the first interim analysis is performed when approximately 368 OS events are observed (i.e. 70% of the total target death events), 3) the second interim analysis is performed when approximately 463 OS events are observed (i.e. 88% of the total target death events), and 4) Lan-DeMets spending function with O'Brien-Fleming boundary is used.

The final PFS analysis is planned to be performed at the time of the first OS interim analysis (IA1) at 27 months after the first participant is randomized. A total of 564 PFS events are estimated to be observed to detect a statistically significant difference at 0.0005 level with >99% power under the assumption that the hazard ratio is 0.55 (median PFS is 7.3 months in Arm A and 4 months in Arm B).

Following Amendment 08, the pre-planned IA2 is no longer required and will not be performed; further details are described in Section 9.1.

9.10 Subgroup Analyses

Both efficacy and safety may be analyzed for the following subgroups as appropriate. For efficacy endpoints, the hazard ratio and two-sided 95% confidence interval (CI) for comparing PFS as assessed by BICR and OS of Arm A vs. Arm B will be presented in forest plots for the subgroups. Median PFS and 95% CIs will be presented for all subgroups. Similar plots will be provided for OS. For safety endpoints, all TEAEs, TEAEs of CTCAE Grades 3 and 4, and treatment-emergent SAEs will be summarized by the subgroups.

- Age group (<65 years vs. ≥65 years)
- Race (White, Asian, Other)
- Geographic region (Region 1: Europe, USA, Canada, Australia, New Zealand, and Israel or Region 2: rest of the world)
- MMR Status (pMMR, dMMR)

9.11 Compliance (Medication Adherence)

Drug accountability data for study treatment will be collected during the study. Any deviation from protocol-directed administration will be reported.

9.12 Extent of Exposure

The extent of exposure for lenvatinib will be summarized as duration of treatment in days. The extent of exposure for pembrolizumab will be summarized as duration of treatment in cycles. Dose interruption for each drug, dose reduction for lenvatinib will be summarized. Summary statistics will be provided on Extent of Exposure for the APaT population.

10. Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical and Study Oversight Considerations

Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)
Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (e.g., International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct or serious GCP-non-compliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and

conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or representative), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is MSD's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by MSD in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor or MSD to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by MSD. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor or MSD in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

Data Protection

Participants will be assigned a unique identifier by MSD. Any participant records or datasets that are transferred to MSD will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor and MSD in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by MSD, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Confidentiality of Data

By signing this protocol, the investigator affirms to MSD that information furnished to the investigator by MSD will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor, MSD (or Sponsor or MSD representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents in order to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to MSD.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

Confidentiality of IRB/IEC Information

MSD is required to record the name and address of each IRB/IEC that reviews and approves this study. MSD is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

Committees Structure

Scientific Advisory Committee

The Scientific Advisory Committee (SAC) is comprised of both Sponsor and non-Sponsor scientific experts who provide input with respect to study design, interpretation of study results and subsequent peer-reviewed scientific publications.

Joint Executive Oversight Committee

The Joint Executive Oversight Committee (EOC) is comprised of members of Sponsor and MSD Senior Management. The EOC will receive and decide upon any recommendations made by the DMC regarding the study.

Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor and MSD. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (see Section 9.7) and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor and MSD protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor and MSD will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor and MSD will generally support

publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor and MSD, the investigator agrees to submit all manuscripts or abstracts to the Sponsor and MSD before submission. This allows the Sponsor and MSD to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD will review this protocol and submit the information necessary to fulfill these requirements. Entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored or executed by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers or from government programs for procedures included as part of the study reimbursed to the investigator by MSD.

The investigator will promptly inform MSD of any regulatory authority inspection conducted for this study.

The investigator agrees to provide MSD with relevant information from inspection observations/findings to allow MSD to assist in responding to any citations resulting from regulatory authority inspection, and will provide MSD with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this study. The investigator will immediately disclose in writing to MSD if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to MSD or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to MSD by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review and audit at reasonable times by representatives of MSD or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by MSD or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

MSD or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of MSD. No records may be transferred to another location or party without written notification to MSD.

Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Site Closure

MSD, in collaboration with the Sponsor, or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event MSD prematurely terminates a particular study site, MSD will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Contraceptive Guidance and Pregnancy Testing

Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of menses for ≥12 months, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 12 during the protocol-defined time frame in Section 5.1.

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.

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.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment. • NOTE: for purposes of AE definition, study treatment includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor or MSD for human use in this study.

Events meeting the AE definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. • For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose of study treatment without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect." • Any new cancer (that is not a condition of the study). Note: Progression of the cancer under study is not a reportable event. Refer to Section 8.4.5 for additional details.

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.

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.

- 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?

- **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.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study treatment relationship).
  - Yes, there is a reasonable possibility of study treatment relationship:
    There is evidence of exposure to study treatment product. The temporal sequence of the AE onset relative to the administration of study treatment is reasonable. The AE is more likely explained by study treatment than by another cause.
  - No, there is not a reasonable possibility of study treatment relationship:
    Participant did not receive study treatment OR temporal sequence of the AE onset relative to administration of study treatment is not reasonable OR the AE is more likely explained by another cause than study treatment. (Also entered for a participant with overdose without an associated AE.)
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to MSD. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to MSD.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements
- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested MSD to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to MSD within 24 hours of receipt of the information.

Reporting of AEs, SAEs, and Other Reportable Safety Events to MSD

AE, SAE, and other reportable safety event reporting to MSD via electronic data collection tool

• The primary mechanism for reporting to MSD will be the electronic data collection (EDC) tool.
  • Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  • If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  • Reference Section 8.4.1 for reporting time requirements
• The site will enter the SAE data into the electronic system as soon as it becomes available.
• After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
• If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
• Contacts for SAE reporting can be found in the Investigator Trial File Binder (or equivalent).

SAE reporting to MSD via paper CRF
• If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to MSD. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

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.

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:

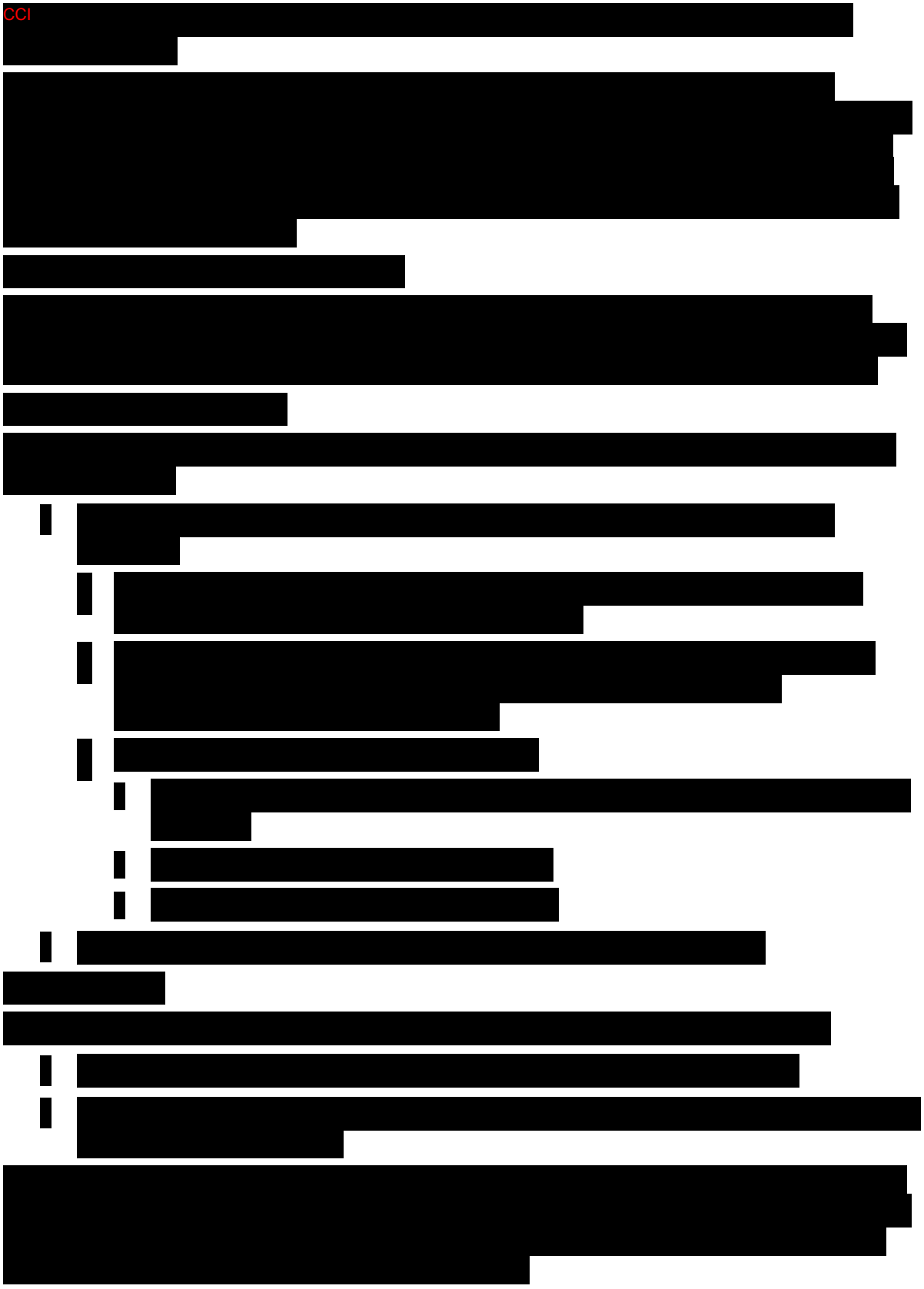
a. Performed only if considered local standard of care.
b. Blood urea nitrogen is preferred; if not available, urea may be tested.
c. Free T4, T3, and TSH levels will be performed during screening and then repeated on Day 1 of every other cycle (starting with Cycle 2), at the time of discontinuation (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.

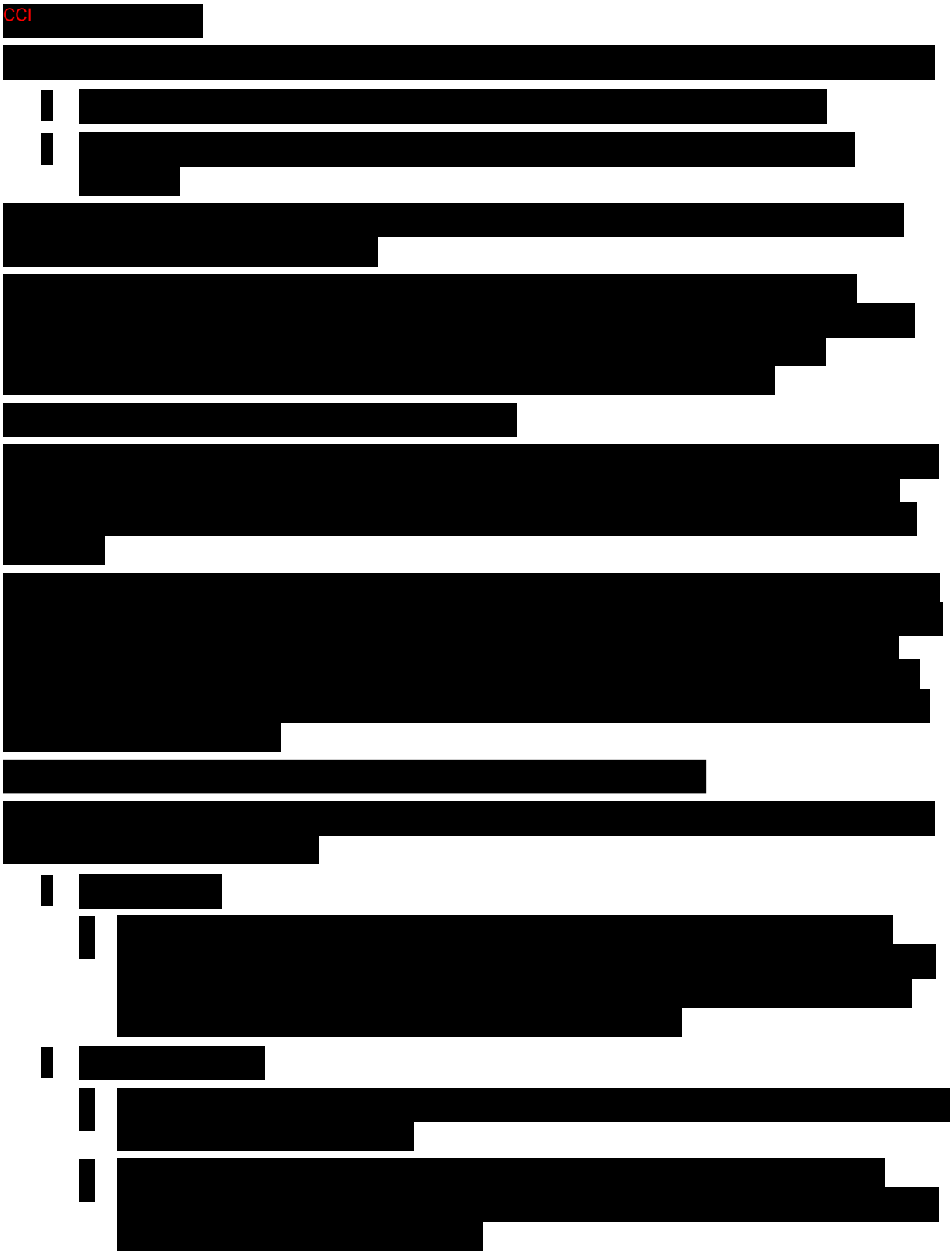
10.5 Appendix 5: CCI [redacted]

CCI [redacted]

CCI



CCI



CCI [redacted]

10.6 Appendix 6: Abbreviations

Abbreviation	Term
AE	Adverse event
AEOSI	Adverse event of special interest
ALT	Alanine aminotransferase
APaT	All Participants as Treated
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BCG	Bacillus Calmette–Guérin
β-hCG	beta-human chorionic gonadotropin
BICR	Blinded independent central review
BP	Blood pressure
C1D1	Cycle 1 Day 1
CCI [redacted]	
CD	Cluster of differentiation
CI	Confidence interval
CIV	Central Imaging Vendor
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA4	Cytotoxic T-lymphocyte-associated protein 4
CYP	Cytochrome P450
CCI [redacted]	
DLT	Dose-limiting toxicity
DMC	Data monitoring committee
dMMR	Mismatch repair deficient
CCI [redacted]	
EC	Endometrial cancer
ECG	Electrocardiogram

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

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

Abbreviation	Term
pMMR	Mismatch repair proficient
PO	Orally
PR	Partial response
PRES/RPLS	Posterior reversible encephalopathy syndrome/reversible posterior leukoencephalopathy syndrome
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QD	Once daily
QLQ-C30	Quality of life Questionnaire C30
QoL	Quality of life
RAG	Recombination activation gene
RBC	Red blood cell
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors
RMST	Restricted Mean Survival Time
RP2D	Recommended Phase 2 dose
RTK	Receptor tyrosine kinase
S6K	S6 kinase
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SoA	Schedule of Activities
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reactions
TAM	Tumor associated macrophage
TEAE	Treatment-emergent adverse event
TPC	Treatment of physician’s choice
ULN	Upper limit of normal
UPCR	Urine protein-to-creatinine ratio
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

Abbreviation	Term
WBRT	whole brain radiation therapy
WOCBP	Woman of childbearing potential

10.7 Appendix 7: Carcinoma of the Endometrium – FIGO Staging

Stage I*	Tumor confined to the corpus uteri
IA*	No or less than half myometrial invasion
IB*	Invasion equal to or more than half of the myometrium
Stage II*	Tumor invades cervical stroma but does not extend beyond the uterus**
Stage III*	Local and/or regional spread of the tumor
IIIA*	Tumor invades the serosa of the corpus uteri and/or adnexa†
IIIB*	Vaginal and/or parametrial involvement†
IIIC*	Metastases to the pelvic and/or para-aortic lymph nodes†
IIIC1*	Positive pelvic nodes
IIIC2*	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV*	Tumor invades bladder and/or bowel mucosa and/or distant metastases
IVA*	Tumor invades the bladder and/or bowel mucosa
IVB*	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

* Either Grade 1, Grade 2, or Grade 3.
** Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II.
† Positive cytology has to be reported separately without changing the stage.

Adapted from Pecorelli S; for the FIGO Committee on Gynecologic Oncology. Int J Gynaecol Obstet. 2009;105(2):103-4 [Pecorelli, S. 2009].

10.8 Appendix 8: New York Heart Association Cardiac Disease Classification

The New York Heart Association (NYHA) Cardiac Disease Classification provides a functional and therapeutic classification for the prescription of physical activity for cardiac participants. On the basis of NYHA definitions, participants are to be classified as follows:

Class	Definition
Class I	Participants with no limitation of activities; they suffer no symptoms from ordinary activities.
Class II	Participants with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
Class III	Participants with marked limitation of activity; they are comfortable only at rest.
Class IV	Participants who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

Adapted from The Criteria Committee of the New York Heart Association, 1994 [Dolgin, M., et al 1994] [Dolgin, M., et al 1994].

10.9 Appendix 9: Country-specific Requirements

Pregnancy Testing

While the protocol allows for more frequent pregnancy testing per the discretion of the investigator, sites should also check with their local health authority to inquire if country-specific guidance regarding the frequency of pregnancy testing is required.

HIV Status

While the protocol does not require specific testing for HIV at Screening, it does require testing if required by the local health authority. Sites should check with their local health authority to inquire if country-specific guidance regarding mandatory HIV testing at Screening is required. This can also be performed per the discretion of the investigator, if desired.

Hepatitis B/C Status

While the protocol does not require specific testing for hepatitis B/C at Screening, it does require testing if required by the local health authority. Sites should check with their local health authority to inquire if country-specific guidance regarding mandatory hepatitis B/C testing at Screening is required. This can also be performed per the discretion of the investigator, if desired.

10.9.1 Germany

HIV testing and hepatitis B/C screening are required evaluations for study entry and need to be performed in order to evaluate eligibility. This testing can be performed at any time during the Screening period.

A pregnancy test will be performed as indicated in the SoA and at least every 30 days up to 120 days post last dose of study medication or the start of a new anticancer therapy, whichever comes first. A pregnancy test is also required at the time of discontinuation (End of Treatment visit).

10.9.2 United Kingdom

HIV testing, and hepatitis B/C screening are required evaluations for study entry and need to be performed in order to evaluate eligibility. This testing can be performed at any time during the Screening period.

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