Official Protocol Title:	A Phase 3 Randomized, Open-Label, Study of Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) Versus Chemotherapy for First-line Treatment of Advanced or Recurrent Endometrial Carcinoma (LEAP-001)
NCT number:	NCT04865289
Document Date:	13-FEBRUARY-2024

Title Page

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Protocol Title: A Phase 3 Randomized, Open-Label, Study of Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) Versus Chemotherapy for First-line Treatment of Advanced or Recurrent Endometrial Carcinoma (LEAP-001)

Protocol Number: 001-07 (E7080-G000-313; ENGOT-EN9)

Compound Number: MK-7902 (E7080/lenvatinib) and MK-3475 (pembrolizumab)

Sponsor Name:

Merck Sharp & Dohme LLC
(hereafter referred to as the Sponsor or MSD)

The study is co-funded by MSD and Eisai.

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	139875
EU CT	2023-505614-17
EudraCT	2018-003009-24

Approval Date: 13 February 2024

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

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.

Typed Name: Title:	Date:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 7	13-FEB-2024	To allow eligible participants on study completion to transition to an extension study in which they can continue to receive pembrolizumab monotherapy, lenvatinib monotherapy, or a combination of both pembrolizumab and lenvatinib as received in the parent study.
Amendment 6	08-JUL-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Amendment 5	17-MAR-2021	To increase the number of participants in the study from approximately 720 to approximately 875.
Amendment 4	15-APR-2020	To expand the participant population to include participants who have received adjuvant or neoadjuvant chemotherapy.
Amendment 3	09-DEC-2019	To include protocol eligibility assessment requirements specific to Germany.
Amendment 2	31-MAY-2019	To include justification for overall survival (OS) non-inferiority margin in response to a request from the European Medicines Agency's Committee for Medicinal Products for Human Use and to provide clarification and program alignment.
Amendment 1	30-JAN-2019	The FDA requested discontinuation from study intervention of participants meeting criteria for elevated liver enzymes.
Original Protocol	19-NOV-2018	Not applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 07

Overall Rationale for the Amendment:

To allow eligible participants on study completion to transition to an extension study in which they can continue to receive pembrolizumab monotherapy, lenvatinib monotherapy, or a combination of both pembrolizumab and lenvatinib as received in the parent study.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
4.4 Beginning and End of Study Definition	Added text to indicate that upon study completion, eligible participants may be enrolled in an extension study in which they are administered pembrolizumab monotherapy, lenvatinib monotherapy, or a combination of both pembrolizumab and lenvatinib as received in the parent study.	This change was made to address a study extension. On study completion, it enables eligible participants to transition to an extension study in which they can continue to receive pembrolizumab monotherapy, lenvatinib monotherapy, or a combination of both pembrolizumab and lenvatinib as received in the parent study.
Additional Changes		
1.3.1 Schedule of Activities – Initial Treatment Phase	Moved chemistry, hematology, and urinalysis panel assessments from Cycle 2 Day 8 to Cycle 2 Day 15.	To remove a typographical error indicating chemistry, hematology, and urinalysis panels should be performed on Cycle 2 Day 8 (which is a telephone contact) instead of Cycle 2 Day 15.
	Added a note to indicate that the collection of Blood for Plasma Biomarker Samples will be discontinued following the implementation of Amendment 07.	Sufficient PRO, plasma biomarker, and circulating tumor nucleic acid data have been collected for analysis for >2 years beyond the last participant enrolled, and further data is not needed.
	Added a note to indicate that the collection of Blood for circulating tumor nucleic acids will be discontinued following the implementation of Amendment 07.	Refer to Section 1.3.1 rationale (removal of biomarker samples).
	Added a note to indicate that the collection of PRO data will be discontinued following the implementation of Amendment 07.	Refer to Section 1.3.1 rationale (removal of biomarker samples).
4.4 Beginning and End of Study Definition	Added text to define the local start of study in EEA.	Revision to align with the EU Clinical Trial Regulation No. 536/2014 of the European Parliament and of the Council.
5 Study Population	Added text to indicate that the collection and use of demographic data will adhere to local laws and participant confidentiality guidelines, while supporting the study of the disease, its associated factors, and the investigated IMP.	Refer to Section 4.4 rationale (EU CTR).

Section Number and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Removed a note from Table 3 indicating that laboratory value requirements for treatment eligibility should be adjusted based on local regulations and guidelines for administering specific chemotherapies.	Refer to Section 4.4 rationale (EU CTR).
6.5.2 Prohibited Concomitant Medications	Added text to indicate that systemic glucocorticoids restrictions apply to participants in the lenvatinib plus pembrolizumab arm. Removed the restriction on systemic glucocorticoids for any purpose other than symptom modulation in suspected immunologic etiology AE.	The description prohibiting systemic glucocorticoids is listed twice consecutively without specifying its application to participants in the lenvatinib plus pembrolizumab arm. This allows to clarify that the prohibition of systemic glucocorticoids applies only to the pembrolizumab plus lenvatinib arm and to remove redundant language referring to allowable systemic glucocorticoid use.
6.6.5 Second Course Phase (Retreatment Period)	Modified the eligibility for the second course phase from BICR-determined to investigator-determined radiographic disease progress.	Sufficient centrally confirmed radiographic progression data has been collected for analysis for >2 years beyond the last participant enrolled and further BICR data is not needed for participants to be eligible for second course.
6.7 Intervention After the End of the Study	Modified text to indicate that upon study completion, participants may be enrolled in an extension study in which they are administered pembrolizumab, lenvatinib, or both lenvatinib and pembrolizumab.	Refer to rationale for primary reason for amendment.
8.2.1.5 RECIST 1.1 Assessment of Disease	Added text to indicate that if disease progression is not verified and the participant is clinically stable, then the study intervention can be continued per protocol at investigator discretion. Removed text indicating that communication with the Sponsor is required before stopping study intervention or imaging or starting a new anticancer therapy in a participant who is clinically stable.	Sufficient centrally confirmed radiographic progression data has been collected for analysis for >2 years beyond the last participant enrolled, and Sponsor consultation is no longer needed before participants discontinue.
8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events	Added text that investigators need to document if an SAE was associated with a medication error, misuse, or abuse.	Refer to Section 4.4 rationale (EU CTR).
8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information	Added text to clarify that from parent study randomization to extension study informed consent signing, reportable safety events and laboratory values must be reported by the investigator per parent study protocol. After extension study, informed consent signing, reportable safety events and laboratory values will be reported by the investigator per extension study protocol.	Refer to rationale for primary reason for amendment.

Section Number and Name	Description of Change	Brief Rationale
8.5 Treatment of Overdose	Added text to indicate that participant should be observed closely for signs of toxicity in the event of an overdose and that appropriate supportive treatment should be provided if clinically indicated.	Refer to Section 4.4 rationale (EU CTR).
8.9 Biomarkers	Added text to indicate that the collection of blood for plasma biomarker samples and blood for circulating tumor nucleic acids will be discontinued following the implementation of Amendment 07.	Refer to Section 1.3.1 rationale (removal of biomarker samples).
9.5 Analysis Population	Modify text to indicate that the China Cohort may also be analyzed separately per local regulatory requirement.	Clarify to align with contents in other sections.
9.7.2 Efficacy Interim Analyses	Added text to indicate that the final analysis for participants enrolled in China may occur at the same time as the final analysis for the global study.	To allow the Final Analysis for participants enrolled in China to occur at the same time as the Global Study Final Analysis.
10.3.1 Definitions of Medication Error, Misuse, and Abuse	Added a new section with definitions of medication error, misuse, and abuse.	Refer to Section 4.4 rationale (EU CTR).
Throughout document	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3 Randomized, Open-Label, Study of Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) Versus Chemotherapy for First-line Treatment of Advanced or Recurrent Endometrial Carcinoma (LEAP-001)

Short Title: Phase 3 study of pembrolizumab plus lenvatinib in endometrial carcinoma

Acronym: LEAP-001

Hypotheses, Objectives, and Endpoints:

In women with Stage III, Stage IV, or recurrent endometrial carcinoma who have been treated with pembrolizumab plus lenvatinib versus chemotherapy:

Primary Objectives	Primary Endpoints
Objective: To compare progression-free survival (PFS) per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) by blinded independent central review (BICR), modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ (see Section 8.2.1). Hypothesis 1 (H1): The combination of pembrolizumab plus lenvatinib is superior to chemotherapy with respect to PFS per RECIST 1.1 by BICR in mismatch repair proficient (pMMR) participants. H2: The combination of pembrolizumab plus lenvatinib is superior to chemotherapy with respect to PFS per RECIST 1.1 by BICR in all-comers.	PFS is defined as the time from randomization to first documented disease progression or death due to any cause, whichever occurs first.
Objective: To compare overall survival (OS) H3: The combination of pembrolizumab plus lenvatinib is non-inferior to chemotherapy with respect to OS in pMMR participants. H4: The combination of pembrolizumab plus lenvatinib is superior to chemotherapy with respect to OS in pMMR participants. H5: The combination of pembrolizumab plus lenvatinib is superior to chemotherapy with respect to OS in all-comers.	OS is defined as the time from randomization to death due to any cause.

Secondary Objectives	Secondary Endpoints
Objective: To compare objective response rate (ORR) per RECIST 1.1 by BICR in pMMR participants and in all-comer participants who have measurable disease at study entry.	Objective Response (OR) is defined as a confirmed complete response (CR) or partial response (PR).
Objective: To evaluate the impact of treatment on Health-Related Quality-of-Life (HRQoL) as assessed by using the global score of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core-30 (QLQ-C30) in pMMR and in all-comer participants.	Mean change from baseline in EORTC QLQ-C30 global health status/quality of life score.
Objective: To compare the safety and tolerability of pembrolizumab plus lenvatinib versus chemotherapy in all-comer participants.	• AEs, SAEs and irAEs. • Study intervention discontinuations due to AEs.

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Participants with advanced or recurrent endometrial carcinoma
Population	Participants with Stage III, Stage IV, or recurrent endometrial carcinoma
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Active
Study Blinding	Unblinded Open-label
Masking	Outcomes Assessor
Estimated Duration of Study	The Sponsor estimates that the Global study will require approximately 51 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit. **Extension Portion of the Study in China:** The study may remain open longer than 51 months to complete an extension portion of the study in China

Number of Participants:

Approximately 875 participants will be randomized to the global portion of this study. After enrollment of the global portion of the study is complete, the study may remain open to enrollment in China alone until the target number of participants from China have been enrolled to meet local regulatory requirements.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Arm 1	Lenvatinib	20 mg	Daily	Oral	Once daily	Test Product
	Pembrolizumab	200 mg	Every 3 weeks (Q3W)	Intravenous (IV) Infusion	Day 1 of each cycle	Test Product
Arm 2	Paclitaxel[a,b]	175 mg/m^2	Q3W	IV Infusion	Day 1 of each cycle	Comparator
	Carboplatin[a]	AUC 6 mg/mL/ min	Q3W	IV Infusion	Day 1 of each cycle	Comparator

Abbreviations: AE=adverse event; IV=intravenous; Q3W=every 3 weeks.

[a] Lower starting dose of paclitaxel (135 mg/m^2) and carboplatin (AUC 5 mg/mL/min) may be administered for participants who are at risk for developing toxicities due to prior pelvic/spine radiation. An AUC 5 mg/mL/min dose for carboplatin may be administered in accordance with local practice.

[b] Docetaxel may be considered for participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel only after consultation with the Sponsor.

Total Number	2 treatment groups

Duration of Participation	Each participant will participate in the study from the time the participant signs the Informed Consent Form through the final protocol-specified contact. After a screening phase of up to 28 days, each participant will be assigned to receive study intervention until one of the conditions for discontinuation of study intervention is met. Participants in Arm 1 who stop study intervention after receiving 35 infusions of pembrolizumab for reasons other than disease progression or intolerability, or participants who attain a complete response (CR) and stop study intervention after a minimum of 8 infusions of pembrolizumab (and a minimum of 2 infusions after the complete response was attained) may be eligible for up to an additional 1 year (17 cycles) of pembrolizumab ± lenvatinib after experiencing disease progression; if lenvatinib is stopped due to unacceptable toxicity, it will not be restarted during second course (Second Course Phase; Section 6.6.5). *Note: Participants who discontinue pembrolizumab after receiving 35 infusions or attaining a CR should continue to receive lenvatinib alone until disease progression is verified by BICR or the development of unacceptable toxicity.* 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 from treatment for reasons other than radiographic disease progression will have posttreatment follow-up imaging to assess disease status until disease progression is documented radiographically per RECIST 1.1 and verified by BICR (and when clinically appropriate, confirmed by the site per iRECIST), initiating a new anticancer treatment, withdrawing consent, becoming lost to follow-up, pregnancy, or death. All participants will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study. Upon study completion, participants are to be discontinued and may be enrolled in an extension study in which they are administered pembrolizumab monotherapy, lenvatinib monotherapy, or a combination of both pembrolizumab and lenvatinib as received in the parent study, if available.

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1.	

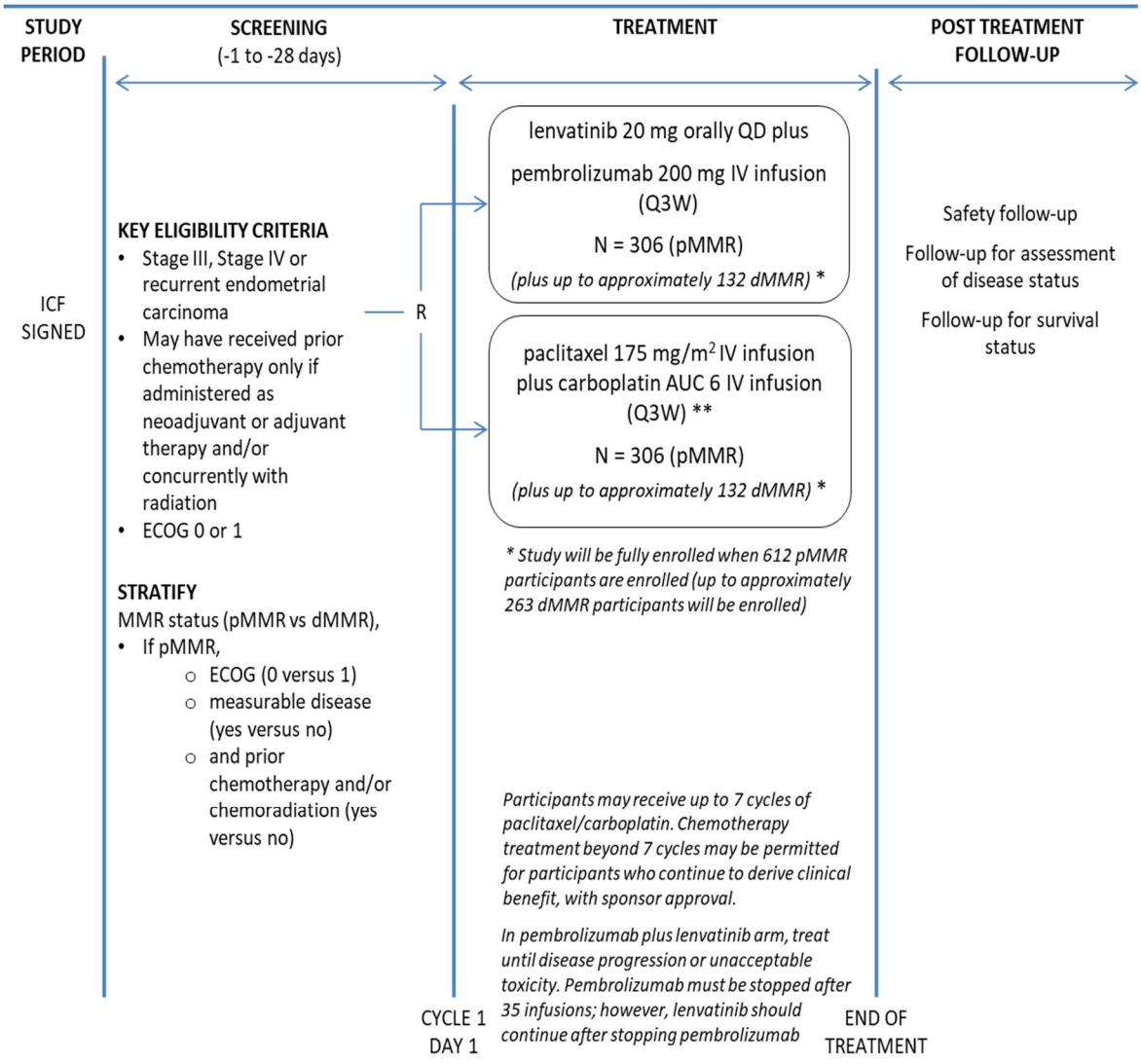
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 13.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Diagram



AE=adverse event; AUC=area under the concentration-time curve; dMMR=mismatch repair deficient; ECOG=Eastern Cooperative Oncology Group; ICF=informed consent form; pMMR=mismatch repair proficient; Q3W=every 3 weeks.

Note: Docetaxel may be considered for participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel only after consultation with the Sponsor (see Section 4.3.3.1)

1.3 Schedule of Activities (SoA)

1.3.1 Schedule of Activities – Initial Treatment Phase

Table 1 Study Schedule of Activities – Initial Treatment Phase

Study Period	**Screen-ing**	**INITIAL Treatment Phase**										**End of Treat-ment**	**Posttreatment**			**Comments**
Treatment Cycle		**C1**			**C2**			**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[b,c]**	**Imaging Follow-up[d]**	**Survival Follow-up**	
Cycle Day		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**	**1**		**30 days and 90 days from last dose (+7)**	**Q9W or Q12W (±7)**	**Q12W (±7)**	
Scheduled Days	**-28 to -1**	**-3[a]**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of discon-tinuation**				
Administrative Procedures																
Informed Consent	X															ICF may be signed at any point prior to performing protocol-specific screening procedures. If MMR result is unavailable within 28 days from when original consent was obtained, an extension may be granted after consultation with the Sponsor as long as all other screening procedures are performed within the protocol-specified timeframe. If the investigator plans to treat beyond the initial radiographic disease progression per RECIST 1.1, additional consent is required at initial site-assessed radiographic disease progression.

Study Period	**Screening**	**INITIAL Treatment Phase**										**End of Treatment**	**Posttreatment**			**Comments**
Treatment Cycle		**C1**			**C2**			**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[b,c]**	**Imaging Follow-up[d]**	**Survival Follow-up**	
Cycle Day		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**	**1**		**30 days and 90 days from last dose (+7)**	**Q9W or Q12W (±7)**	**Q12W (±7)**	
Scheduled Days	**-28 to -1**	**-3[a]**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of discontinuation**				
Inclusion/Exclusion Criteria	X															
Participant Identification Card	X	X														Add randomization number at C1.
Demographics	X															
Medical History	X															Significant medical history to be captured for last 10 years.
Endometrial Carcinoma History	X															Review prior surgery, radiation and oncologic therapy.
FIGO Staging at Initial Diagnosis	X															
Prior/Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X			Record medications taken within 28 days prior to the start of study intervention. Concomitant medications will be recorded for 30 days after last dose (or for up to 120 days after last dose for SAEs).
Randomization and Study Intervention Assignment		X														Participants may be randomized up to 3 days prior to C1D1. All C1D1 procedures and assessments should be performed after randomization.

Study Period	**Screen-ing**	**INITIAL Treatment Phase**										**End of Treat-ment**	**Posttreatment**			**Comments**
Treatment Cycle		**C1**			**C2**			**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[b,c]**	**Imaging Follow-up[d]**	**Survival Follow-up**	
Cycle Day		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**	**1**					
Scheduled Days	**-28 to -1**	**-3[a]**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of discon-tinuation**	**30 days and 90 days from last dose (+7)**	**Q9W or Q12W (±7)**	**Q12W (±7)**	
Telephone Contact			X			X										A phone visit will be scheduled to report blood pressure and record adverse events. Blood pressure will be taken, for example, at home or at a local pharmacy, and will be reviewed with the investigator or designee. Note: An unscheduled clinic visit can occur prior to C1D15 or C2D15 if necessary for safety.
Review New Anticancer Treatment												X	X	X	X	All anticancer therapy will be recorded until time of death or termination of survival follow-up. If a clinical visit is not feasible, this information may be obtained via telephone or e-mail.
Survival Status			←								→				X	All participants may be contacted for survival status at any time during the course of the study.

Study Period	**Screen-ing**	**INITIAL Treatment Phase**										**End of Treat-ment**	**Posttreatment**			**Comments**
Treatment Cycle		**C1**			**C2**			**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[b,c]**	**Imaging Follow-up[d]**	**Survival Follow-up**	
Cycle Day		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**	**1**		**30 days and 90 days from last dose (+7)**	**Q9W or Q12W (±7)**	**Q12W (±7)**	
Scheduled Days	**-28 to -1**	**-3[a]**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of discon-tinuation**				
Clinical Assessments or Procedures																
AE/SAE review	X	X	X	X	X	X	X	X	X	X	X	X	X	X		AEs: monitored up to 90 days after last dose or 30 days after the last dose if the participant initiates new anticancer therapy, whichever occurs first. SAEs: monitored up to 120 days after last dose, or 30 days after last dose if participant starts a new anticancer therapy, whichever occurs first.
Full Physical Examination	X											X				Includes evaluation of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination.
Directed Physical Examination		X			X			X	X	X	X		X			Based on participant's symptoms.

Study Period	**Screen-ing**	**INITIAL Treatment Phase**										**End of Treat-ment**	**Posttreatment**			**Comments**
Treatment Cycle		**C1**			**C2**			**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[b,c]**	**Imaging Follow-up[d]**	**Survival Follow-up**	
Cycle Day		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**	**1**		**30 days and 90 days from last dose (+7)**	**Q9W or Q12W (±7)**	**Q12W (±7)**	
Scheduled Days	**-28 to -1**	**-3[a]**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of discon-tinuation**				
Vital Signs	X	X		X	X		X	X	X	X	X	X	X			Height at screening only. Refer to Section 8.3.2 for monitoring vital signs and Section 6.6.1.1 for hypertension management and BP monitoring guidelines. Blood pressure should be taken on the day of dosing.
12-lead ECG	X	X			X						X	X	X			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	**Screen-ing**	**INITIAL Treatment Phase**										**End of Treat-ment**	**Posttreatment**			**Comments**
Treatment Cycle		**C1**			**C2**			**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[b,c]**	**Imaging Follow-up[d]**	**Survival Follow-up**	
Cycle Day		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**	**1**		**30 days and 90 days from last dose (+7)**	**Q9W or Q12W (±7)**	**Q12W (±7)**	
Scheduled Days	**-28 to -1**	**-3[a]**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of discon-tinuation**				
MUGA or ECHO LVEF Assessment	X											X				Additional assessments may be performed as clinically indicated.
NYHA Cardiac Disease Classification	X															See Appendix 10. Only required for participants with cardiovascular impairment within 12 months of the first dose of study intervention.
ECOG Performance Status	X				X			X	X	X	X	X	X			Assess within 7 days prior to first dose of study intervention. Assess prior to treatment during subsequent treatment visits.

Study Period	**Screening**	**INITIAL Treatment Phase**										**End of Treatment**	**Posttreatment**			**Comments**
Treatment Cycle		**C1**			**C2**			**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[b,c]**	**Imaging Follow-up[d]**	**Survival Follow-up**	
Cycle Day		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**	**1**		**30 days and 90 days from last dose (+7)**	**Q9W or Q12W (±7)**	**Q12W (±7)**	
Scheduled Days	**-28 to -1**	**-3[a]**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of discontinuation**				
Laboratory Assessments or Procedures																
Pregnancy Test (WOCBP only) – Urine or β-HCG	X				X			X	X	X	X	X	X	X		WOCBP require: A negative test prior to randomization and within 24 hours prior to the first dose of study intervention. If less than 24 hours have elapsed between the randomization test and the first dose of study intervention, another pregnancy test is not required. Serum or urine pregnancy tests will be performed per Appendix 2. Pregnancy testing should be performed every 30 days during the intervention period and for at least 120 days post pembrolizumab or 30 days post lenvatinib (up to 180 days for participants receiving chemotherapy) or the start of a new anticancer therapy, whichever comes first. In the absence of 12 months of amenorrhea, hysterectomy, or oophorectomy, confirmation with 2 FSH measurements in the postmenopausal range is required.

Study Period	**Screening**	**INITIAL Treatment Phase**										**End of Treatment**	**Posttreatment**			**Comments**
Treatment Cycle		**C1**			**C2**			**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[b,c]**	**Imaging Follow-up[d]**	**Survival Follow-up**	
Cycle Day		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**	**1**					
Scheduled Days	**-28 to -1**	**-3[a]**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of discontinuation**	**30 days and 90 days from last dose (+7)**	**Q9W or Q12W (±7)**	**Q12W (±7)**	
HIV Testing	X															Required prior to enrollment if mandated by local health authority.
Hepatitis B and C Testing	X															Required prior to enrollment if mandated by local health authority.
PT/INR and aPTT/PTT	X															Perform within 7 days prior to first dose of study intervention. Participants receiving coumarin-based anticoagulants should have more frequent INR monitoring as clinically indicated.
Chemistry Panel	X			X	X		X	X	X	X	X	X	X			Perform within 7 days prior to first dose of study intervention.
Hematology Panel	X			X	X		X	X	X	X	X	X	X			Perform within 7 days prior to first dose of study intervention.
Urine Dipstick Testing	X			X	X		X	X	X	X	X	X	X			Perform within 7 days prior to first dose of study intervention. Refer to Section 6.6.1.2 for management of proteinuria by dipstick, UPCR and/or 24-hour urinalysis.

Study Period	**Screen-ing**	**INITIAL Treatment Phase**										**End of Treat-ment**	**Posttreatment**			**Comments**
Treatment Cycle		**C1**			**C2**			**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[b,c]**	**Imaging Follow-up[d]**	**Survival Follow-up**	
Cycle Day		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**	**1**		**30 days and 90 days from last dose (+7)**	**Q9W or Q12W (±7)**	**Q12W (±7)**	
Scheduled Days	**-28 to -1**	**-3[a]**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of discon-tinuation**				
T3, FT4, TSH	X				X				X		X	X	X			Perform within 7 days prior to first dose of study intervention. Perform every other cycle starting with Cycle 2 (C2, C4, C6,…).
Sample Collection																
MMR Status	X															pMMR versus dMMR
Submission of Archival or Newly Obtained Tumor Tissue Blocks or Slides	X															Sample collected for exploring biomarkers of response.
Blood for Genetic Analysis		X														Predose
Blood for RNA Analysis		X			X			X		X		X				Predose on C1D1, C2D1, C3D1, C5D1, and at EOT.
Blood for Serum Biomarkers		X		X	X			X		X		X				Predose on C1D1, C1D15, C2D1, C3D1, C5D1, and at EOT.

Study Period	**Screen-ing**	**INITIAL Treatment Phase**										**End of Treat-ment**	**Posttreatment**			**Comments**
Treatment Cycle		**C1**			**C2**			**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[b,c]**	**Imaging Follow-up[d]**	**Survival Follow-up**	
Cycle Day		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**	**1**					
Scheduled Days	**-28 to -1**	**-3[a]**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of discon-tinuation**	**30 days and 90 days from last dose (+7)**	**Q9W or Q12W (±7)**	**Q12W (±7)**	
Blood for Plasma Biomarkers		X			X			X		X	X	X				Predose on C1D1, C2D1, C3D1, C5D1, on D1 every 3 cycles thereafter (C8D1, C11D1, C14D1,…) and at EOT. The collection of blood for plasma biomarker samples will be discontinued following the implementation of Amendment 07.
Blood for Circulating Tumor Nucleic Acids		X			X			X		X	X	X				Predose on C1D1, C2D1, C3D1, C5D1, on D1 every 3 cycles thereafter (C8D1, C11D1, C14D1,…) and at EOT. The collection of blood for circulating tumor nucleic acids will be discontinued following the implementation of Amendment 07.

Study Period	**Screening**	**INITIAL Treatment Phase**										**End of Treatment**	**Posttreatment**			**Comments**
Treatment Cycle		**C1**			**C2**			**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[b,c]**	**Imaging Follow-up[d]**	**Survival Follow-up**	
Cycle Day		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**	**1**		**30 days and 90 days from last dose (+7)**	**Q9W or Q12W (±7)**	**Q12W (±7)**	
Scheduled Days	**-28 to -1**	**-3[a]**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of discontinuation**				
Health Related Quality of Life																
Perform in this order: EORTC QLQ-C30 EORTC QLQ-EN24 EuroQoL EQ-5D-5L		X			X			X	X	X	X	X	X			Every effort should be made to administer HRQoL surveys prior to dosing and before other assessments and procedures. Collect on Day 1 of every cycle through Cycle 35, then every 4 cycles through Cycle 60, at time of discontinuation, at the 30-day and 90-day Safety Follow-up visit. The collection of PRO data will be discontinued following the implementation of Amendment 07.
Efficacy Measurements																
Imaging Chest/Abdomen/Pelvis	X		X									X		X[e]		Perform within 28 days prior to randomization. On treatment Q9W (±7 days) from randomization through Week 54, Q12W (±7 days) thereafter. If imaging was obtained within 28 days prior to discontinuation, an additional scan is not needed at discontinuation.

Study Period	**Screen-ing**	**INITIAL Treatment Phase**										**End of Treat-ment**	**Posttreatment**			**Comments**
Treatment Cycle		**C1**			**C2**			**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[b,c]**	**Imaging Follow-up[d]**	**Survival Follow-up**	
Cycle Day		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**	**1**		**30 days and 90 days from last dose (+7)**	**Q9W or Q12W (±7)**	**Q12W (±7)**	
Scheduled Days	**-28 to -1**	**-3[a]**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of discon-tinuation**				
Imaging Bone	X		X									X		X[e]		Perform within 42 days prior to randomization if known to be positive for bone metastases at baseline or if clinically symptomatic. If positive for bone metastases at baseline, continue imaging at W27, W54, and Q24W (±7 days) thereafter (W78, W102, W126…). Bone scan is required ≤2 weeks after CR for all participants positive for bone metastases at any point during the study. If imaging was obtained within 28 days prior to discontinuation, an additional scan is not needed at discontinuation.

Study Period	**Screen-ing**	**INITIAL Treatment Phase**										**End of Treat-ment**	**Posttreatment**			**Comments**
Treatment Cycle		**C1**			**C2**			**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[b,c]**	**Imaging Follow-up[d]**	**Survival Follow-up**	
Cycle Day		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**	**1**		**30 days and 90 days from last dose (+7)**	**Q9W or Q12W (±7)**	**Q12W (±7)**	
Scheduled Days	**-28 to -1**	**-3[a]**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of discon-tinuation**				
Imaging Brain	X		X									X		X[e]		Perform within 28 days prior to randomization if known to have brain metastases at baseline or if clinically symptomatic. If positive for brain metastases at baseline, continue imaging Q9W from randomization through Week 54, Q12W (±7 days) thereafter. Brain imaging is required ≤2 weeks after CR for all participants positive for brain metastases at any point during the study. If imaging was obtained within 28 days prior to discontinuation, an additional scan is not needed at discontinuation.
Dispensing and Administration of Study intervention																
Pembrolizumab (Arm 1)		X			X			X	X	X	X					200 mg IV Q3W up to 35 infusions.
Lenvatinib (Arm 1)		X			X			X	X	X	X					20 mg orally QD until disease progression or unacceptable toxicity.

Study Period	**Screening**	**INITIAL Treatment Phase**										**End of Treatment**	**Posttreatment**			**Comments**
Treatment Cycle		**C1**			**C2**			**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[b,c]**	**Imaging Follow-up[d]**	**Survival Follow-up**	
Cycle Day		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**	**1**		**30 days and 90 days from last dose (+7)**	**Q9W or Q12W (±7)**	**Q12W (±7)**	
Scheduled Days	**-28 to -1**	**-3[a]**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of discontinuation**				
Paclitaxel/carboplatin (Arm 2)[f, g]		X			X			X	X	X	X					Paclitaxel: 175 mg/m^2 IV Q3W up to 7 cycles. Carboplatin: AUC 6 mg/mL/min IV Q3W up to 7 cycles (administered immediately after paclitaxel).

Abbreviations: AE=adverse event; BICR=blinded independent central review; BP=blood pressure; C1=Cycle 1; C2 = Cycle 2; CR=complete response; CT=computed tomography; D1=Day 1; D8=Day 8; D15=Day 15; DC=discontinuation; dMMR=mismatch repair deficient; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC QLQ=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EOT=End of Treatment; EQ-5D-5L=EuroQoL 5-dimension, 5-level Questionnaire; 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; IRT=interactive response technology; LVEF=left ventricular ejection fraction; MMR=mismatch repair; MRI=magnetic resonance imaging; MUGA=multigated acquisition; nAb=neutralizing antibodies; NYHA=New York Heart Association; PD=progressive disease; PFS2=progression-free survival on next-line therapy; pMMR=mismatch repair proficient; Q3W=every 3 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; Q24W=every 24 weeks; QD=once daily; QW=every week; RNAseq=RNA sequencing; RR=respiratory rate; SAE=serious adverse event; T3=triiodothyronine; TSH=thyroid stimulating hormone; WES=whole exome sequencing; WOCBP=women of childbearing potential.

a. With the exception of ECGs, and blood pressure (which should be performed on the day of dosing), C1D1 assessments can be performed up to 3 days prior to dosing. The screening assessment can serve as the C1D1 assessment if performed within 72 hours prior to randomization.

b. If a discontinuation visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up visit is not required. All procedures for both visits will be performed at the discontinuation visit.

c. The 90-day Safety Follow-up visit is only required for participants who have not yet started new anticancer treatment. If the 90-day Safety Follow-up visit falls within the same window as an imaging follow-up visit, the procedures required at both visits may be combined.

d. Follow-up visits to be scheduled to coincide with follow-up imaging.

e. 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, confirmed by the site per iRECIST when clinically appropriate, initiating a new anticancer treatment, withdrawing consent, becoming lost to follow-up, pregnancy or death.

f. A lower starting dose of paclitaxel (135 mg/m^2) and carboplatin (AUC 5 mg/mL/min) may be administered for participants who are at risk for developing toxicities due to prior pelvic/spine radiation. An AUC 5 mg/mL/min dose for carboplatin may be administered in accordance with local practice. Docetaxel may be considered for

Study Period	**Screen-ing**	**INITIAL Treatment Phase**										**End of Treat-ment**	**Posttreatment**			**Comments**
Treatment Cycle		**C1**			**C2**			**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[b,c]**	**Imaging Follow-up[d]**	**Survival Follow-up**	
Cycle Day		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**	**1**		**30 days and 90 days from last dose (+7)**	**Q9W or Q12W (±7)**	**Q12W (±7)**	
Scheduled Days	**-28 to -1**	**-3[a]**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of discon-tinuation**				

participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel only after consultation with the Sponsor (see Section 4.3.3.1).

g. Chemotherapy treatment beyond 7 cycles may be permitted for participants who continue to derive clinical benefit, with Sponsor approval.

1.3.2 Schedule of Activities – Second Course Treatment Phase

Table 2 Study Schedule of Activities – Second Course Treatment Phase

Study Period	**SECOND COURSE Treatment Phase**						**End of Treatment**	**Post-Treatment**			**Comments**
Treatment Cycle	**C1**	**C2**	**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[b,c]**	**Imaging Follow-up[d]**	**Survival Follow-up**	
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**	**At time of discon-tinuation**	**30 days and 90 days from last dose (+7)**	**Q12W (±7)**	**Q12W (±7)**	
Scheduled Days	**3[a]**	**±3**	**±3**	**±3**	**±3**	**±3**					
Administrative Procedures											
Review Eligibility Criteria	X										
Review Concomitant Medication	X	X	X	X	X	X	X	X			Record medications taken within 28 days prior to Second Course Cycle 1. Concomitant medications will be recorded for 30 days after last dose (or for up to 120 days after last dose for SAEs).
Review New Anticancer Treatment							X	X	X	X	All anticancer therapy will be recorded until time of death or termination of survival follow-up. If a clinical visit is not feasible, this information may be obtained via telephone or e-mail.
Survival Status	⟷									X	All participants may be contacted for survival status at any time during the course of the study.

Study Period	**SECOND COURSE Treatment Phase**						**End of Treatment**	**Post-Treatment**			**Comments**
Treatment Cycle	**C1**	**C2**	**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[b,c]**	**Imaging Follow-up[d]**	**Survival Follow-up**	
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**	**At time of discon-tinuation**	**30 days and 90 days from last dose (+7)**	**Q12W (±7)**	**Q12W (±7)**	
Scheduled Days	**3[a]**	**±3**	**±3**	**±3**	**±3**	**±3**					
Clinical Assessments or Procedures											
AE/SAE review	X	X	X	X	X	X	X	X	X		AEs: monitored up to 90 days after last dose or 30 days after the last dose if the participant initiates new anticancer therapy, whichever occurs first. SAEs: monitored up to 120 days after last dose, or 30 days after last dose if participant starts a new anticancer therapy, whichever occurs first.
Full Physical Exam	X						X				Includes evaluation of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination.
Directed Physical Exam		X	X	X	X	X		X			Exam based on participant's symptoms.
Vital Signs	X	X	X	X	X	X	X	X			Refer to Section 8.3.2 for monitoring vital signs and Section 6.6.1.1 for hypertension management and BP monitoring guidelines.

Study Period	**SECOND COURSE Treatment Phase**						**End of Treatment**	**Post-Treatment**			**Comments**
Treatment Cycle	**C1**	**C2**	**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[b,c]**	**Imaging Follow-up[d]**	**Survival Follow-up**	
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**	**At time of discon-tinuation**	**30 days and 90 days from last dose (+7)**	**Q12W (±7)**	**Q12W (±7)**	
Scheduled Days	**3[a]**	**±3**	**±3**	**±3**	**±3**	**±3**					
12-lead ECG	X	X				X	X	X			Required at C1D1 prior to restarting study intervention unless it was already completed within 28 days prior to Second Course Cycle 1. Also required at C2D1, D1 of every 4th cycle (12 weeks) thereafter (eg, C6, C10, C14, etc.), EOT, and safety follow-up. For high-risk participants (as defined in Sec. 8.3.3), conduct ECG monitoring every cycle (if on lenvatinib). If lenvatinib is discontinued, ECGs are only required at the EOT and Safety Follow-up visits.
MUGA or ECHO LVEF Assessment	X						X				Required prior to restarting study intervention only if it was not already completed within 28 days prior. Additional assessments may be performed as clinically indicated.
ECOG Performance Status	X	X	X	X	X	X	X				Perform within 3 days prior to Second Course Cycle 1. Assess prior to treatment during subsequent treatment visits.

Study Period	**SECOND COURSE Treatment Phase**						**End of Treatment**	**Post-Treatment**			**Comments**
Treatment Cycle	**C1**	**C2**	**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[b,c]**	**Imaging Follow-up[d]**	**Survival Follow-up**	
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**	**At time of discon-tinuation**	**30 days and 90 days from last dose (+7)**	**Q12W (±7)**	**Q12W (±7)**	
Scheduled Days	**3[a]**	**±3**	**±3**	**±3**	**±3**	**±3**					
Laboratory Assessments or Procedures											
Pregnancy Test (WOCBP only) - Urine or β-HCG	X	X	X	X	X	X	X	X	X		For WOCBP, perform within 24 hours prior to Second Course Cycle 1. Pregnancy testing should be performed every 30 days during the intervention period and for at least 120 days post pembrolizumab or 30 days post lenvatinib or the start of a new anticancer therapy, whichever comes first.
PT/INR and aPTT/PTT	X										Perform within 3 days prior to Second Course Cycle 1 Participants receiving coumarin-based anticoagulants should have more frequent INR monitoring as clinically indicated.
Chemistry Panel	X	X	X	X	X	X	X	X			Perform within 3 days prior to Second Course Cycle 1
Hematology Panel	X	X	X	X	X	X	X	X			Perform within 3 days prior to Second Course Cycle 1.
Urine Dipstick Testing	X	X	X	X	X	X	X	X			Perform within 3 days prior to Second Course Cycle 1. Refer to Section 6.6.1.2 for management of proteinuria by dipstick, UPCR and/or 24-hour urinalysis.
T3, FT4, TSH	X		X		X		X	X			Perform within 3 days prior to Second Course Cycle 1 and every other cycle thereafter (C3, C5, C7,…).

Study Period	**SECOND COURSE Treatment Phase**						**End of Treatment**	**Post-Treatment**			**Comments**
Treatment Cycle	**C1**	**C2**	**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[b,c]**	**Imaging Follow-up[d]**	**Survival Follow-up**	
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**	**At time of discon-tinuation**	**30 days and 90 days from last dose (+7)**	**Q12W (±7)**	**Q12W (±7)**	
Scheduled Days	**3[a]**	**±3**	**±3**	**±3**	**±3**	**±3**					
Efficacy Measurements											
Imaging Chest/Abdomen/Pelvis	X	X					X		X[e]		Perform within 28 days prior to Second Course Cycle 1. Q12W (±7 days) from Second Course Cycle 1 onwards or more frequently as clinically indicated. If imaging was obtained within 28 days prior to discontinuation, an additional scan is not needed at discontinuation.
Imaging Brain	X	X					X		X[e]		Perform within 28 days prior to Second Course Cycle 1 for participants known to be positive for brain metastases or who are clinically symptomatic. If positive for brain metastases at the start of Second Course, continue imaging Q12W (±7 days) from Second Course Cycle 1 onwards or more frequently as clinically indicated. If imaging was obtained within 28 days prior to discontinuation, an additional scan is not needed at discontinuation.

Study Period	**SECOND COURSE Treatment Phase**						**End of Treatment**	**Post-Treatment**			**Comments**
Treatment Cycle	**C1**	**C2**	**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[b,c]**	**Imaging Follow-up[d]**	**Survival Follow-up**	
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**	**At time of discon-tinuation**	**30 days and 90 days from last dose (+7)**	**Q12W (±7)**	**Q12W (±7)**	
Scheduled Days	**3[a]**	**±3**	**±3**	**±3**	**±3**	**±3**					
Imaging Bone	X	X					X		X[e]		Perform within 42 days prior to Second Course Cycle 1 for participants known to be positive for bone metastases or who are clinically symptomatic. If positive for bone metastases at the start of Second Course, continue imaging Q24W (±7 days) from Second Course Cycle 1 onwards, or more frequently as clinically indicated. If imaging was obtained within 28 days prior to discontinuation, an additional scan is not needed at discontinuation.
Dispensing and Administration of Study intervention											
Pembrolizumab	X	X	X	X	X	X					200 mg IV Q3W up to 17 additional cycles
Lenvatinib	X	X	X	X	X	X					If receiving lenvatinib in Second Course, start with the last prescribed dose last taken in First Course. If lenvatinib is stopped due to unacceptable toxicity in First Course, it will not be restarted during Second Course.

Study Period	**SECOND COURSE Treatment Phase**						**End of Treatment**	**Post-Treatment**			**Comments**
Treatment Cycle	**C1**	**C2**	**C3**	**C4**	**C5**	**C6+**		**Safety Follow-up[b,c]**	**Imaging Follow-up[d]**	**Survival Follow-up**	
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**	**At time of discon-tinuation**	**30 days and 90 days from last dose (+7)**	**Q12W (±7)**	**Q12W (±7)**	
Scheduled Days	**3[a]**	**±3**	**±3**	**±3**	**±3**	**±3**					

Abbreviations: AE=adverse event; BICR=blinded independent central review; BP=blood pressure; C1=Cycle 1; C2=Cycle 2; CR=complete response; CT=computed tomography; D1=Day 1; D8=Day 8; D15=Day 15; DC=discontinuation; 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; IRT=interactive response technology; LVEF=left ventricular ejection fraction; MMR=mismatch repair; MRI=magnetic resonance imaging; MUGA=multigated acquisition; nAb=neutralizing antibodies; NYHA=New York Heart Association; PD=progressive disease; PFS2=progression-free survival on next-line therapy; Q3W=every 3 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; Q24W=every 24 weeks; QD=once daily; QW=every week; RNAseq=RNA sequencing; RR=respiratory rate; SAE=serious adverse event; T3=triiodothyronine; TSH=thyroid stimulating hormone; WES=whole exome sequencing; WOCBP=women of childbearing potential.

a. With the exception of ECGs and blood pressure (which should be performed on the day of dosing), C1D1 assessments can be performed up to 3 days prior to dosing. The screening assessment can serve as the C1D1 assessment if performed within 72 hours prior to randomization.

b. If discontinuation visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up visit is not required. All procedures for both visits will be performed at the discontinuation visit.

c. The 90-day Safety Follow-up visit is only required for participants who have not yet started new anticancer treatment. If the 90-day Safety Follow-up visit falls within the same window as an imaging follow-up visit, the procedures required at both visits may be combined.

d. Follow-up visits to be scheduled to coincide with follow-up imaging.

e. 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, confirmed by the site per iRECIST when clinically appropriate, initiating a new anticancer treatment, withdrawing consent, becoming lost to follow-up, pregnancy or death.

2 INTRODUCTION

2.1 Study Rationale

Carcinoma of the uterine corpus is often referred to as endometrial cancer (EC) because the vast majority of cases (~92%) occur in the endometrium (lining of the uterus) [American Cancer Society 2018]. Most EC cases are identified at an early stage with a 5-year survival rate of 94.9% for localized EC [National Cancer Institute 2018]. However, despite early detection, approximately 13% of all endometrial carcinomas recur [Fung-Kee-Fung, M., et al 2006]. Women diagnosed with advanced or recurrent disease have a poor prognosis, with a 5-year survival rate of 17% [National Cancer Institute 2018] [Makker, V., et al 2017].

The combination of immune checkpoint inhibitor pembrolizumab and lenvatinib (a multi receptor tyrosine kinase inhibitor) has emerged as a novel combination with promising efficacy in EC. KEYNOTE-146/E7080-A001-111 (Study 111) is an ongoing Phase 1b/2 study that is being conducted in selected solid tumors, including EC. Promising activity was observed in 53 EC participants who had progressed on prior therapy and showed an ORR of 39%, and response was seen across participants who had both defective mismatch repair and proficient mismatch repair. Based on the data from Study 111, the present study has been designed to compare the combination of pembrolizumab and lenvatinib (also known as E7080 or MK-7902, hereafter referred to as lenvatinib), to paclitaxel and carboplatin in patients with newly diagnosed Stage III, Stage IV, or recurrent EC.

2.2 Background

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's Brochure.

Lenvatinib (also known as E7080 or MK 7902; hereafter referred to as lenvatinib) inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors (VEGFRs), 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 (FGFRs), FGFR1, FGFR2, FGFR3, and FGFR4, platelet-derived growth factor receptor (PDGFR) α, c-kit, and the *RET* proto-oncogene. Lenvatinib also showed antiproliferative activity in cell lines dependent on activated FGFR signaling with a concurrent inhibition of FGFR substrated 2α phosphorylation.

Refer to the Investigator's Brochures (IBs)/approved labeling for detailed background information on pembrolizumab [IB Edition 17 2019] and lenvatinib [IB Edition 16 2019].

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 Pembrolizumab

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 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 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. After 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 CD3ζ, PKCθ, and 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 EC.

2.2.1.2 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. and Hicklin, D. J. 2008] [Tammela, T. and Alitalo, K. 2010]. Accumulated evidence suggests that FGF and its receptor tyrosine kinase, FGFR also play important roles for tumor angiogenesis [Cross, M. J. and Claesson-Welsh L. 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 Ki 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 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 MAPK pathway and the mTOR-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 showed 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), RCC, HCC, melanoma, gastric 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 human umbilical vein endothelial cell (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.

2.2.1.3 Endometrial Carcinoma: Epidemiology and Current Therapeutic Options

Endometrial cancer is the sixth most common cancer in women worldwide with approximately 320,000 new cases diagnosed in 2012 [Ferlay, J., et al 2015] [Torre, L. A., et al 2017]. In the United States, the estimated numbers of new cases and deaths occurring in 2018 are 63,230 and 11,350, respectively [National Cancer Institute 2018]. Chemotherapy has been the standard of care in the first-line treatment setting and beyond, with platinum compounds, anthracyclines, and taxanes (alone and in combination) being the most frequently used treatments for women with advanced or recurrent EC [National Comprehensive Cancer Network 2017] [Colombo, N., et al 2013] [Miller, D., et al 2015]. While systemic therapy has improved outcomes in the first-line treatment setting [Thigpen, J. T., et al 1994] [Thigpen, J. T., et al 2004] [Fleming, G. F., et al 2004], the median progression-free survival and overall survival remains at 14 months and 32 to 38 months respectively [Miller, D., et al 2015] suggesting an urgent need for newer systemic therapies.

An interim analysis of 1,381 (69 ineligible) participants who received first-line chemotherapy for metastatic or recurrent EC showed that the combination of paclitaxel and carboplatin (TC) chemotherapy was not clinically inferior to the combination of doxorubicin, cisplatin, and paclitaxel (TAP) chemotherapy with regard to PFS (median TC versus TAP, 14 versus 14 months; Hazard Ratio [HR] = 1.03) and OS (median TC versus TAP, 32 versus 38 months; HR = 1.01) [Miller, D., et al 2015]. Overall, the toxicity profile favored TC and study intervention was discontinued due to toxicity in 18% on TAP and 12% on TC. Although TC remains a reasonable first-line treatment option, there is a need for treatment that is more efficacious and/or tolerable. 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 (MK-7902-001) will compare the efficacy and safety of lenvatinib in combination with pembrolizumab versus paclitaxel plus carboplatin in participants with advanced EC.

2.2.1.4 Scientific Rationale for the Combination of Lenvatinib with 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 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 renal cell carcinoma. 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].

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/L1 signal inhibitors. The effect of combining lenvatinib with an antihuman PD-1 humanized mAb was investigated in 4 murine tumor isograft models, which showed significant tumor growth inhibition compared with 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 with that of the respective monotherapy groups [Kato, Y., et al 2019]. All treatments were well tolerated and severe body weight loss was not observed

Based on these results, an open-label, Phase 1b/2 study (Study 111) to assess the safety and preliminary antitumor activity of the combination of lenvatinib plus pembrolizumab in participants with selected solid tumors is currently ongoing. Phase 1b of this study determined the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) as 20 mg lenvatinib once daily (QD) in combination with 200 mg of pembrolizumab given IV every 3 weeks (Q3W). The safety and efficacy of the combination at the lenvatinib RP2D is being assessed in the Phase 2 portion of the study that includes 6 cohorts (ie, nonsmall cell lung cancer (NSCLC), renal cell carcinoma (RCC), EC, urothelial carcinoma, melanoma, and squamous cell carcinoma of the head and neck). Based on the tolerable safety profile observed, and promising antitumor efficacy seen in both the EC and RCC expansion cohorts from Study 111/KEYNOTE-146 [Makker, V., et al 2018], 2 Phase 3 studies are ongoing for both of these tumor types, Study E7080-G000-309/KEYNOTE-775 and Study E7080-G000-307/KEYNOTE-581.

2.2.1.5 Rationale for Inclusion of Participants Who Have Received Prior Adjuvant and/or Neoadjuvant Chemotherapy

After resection of localized or locally advanced high-risk endometrial cancer, platinum-based adjuvant chemotherapy is frequently administered to reduce the risk of disease recurrence. The adjuvant chemotherapy may be administered in 3 ways:1) chemotherapy alone; 2) as part of a concurrent chemoradiation regimen; or 3) as part of a sequential approach such as in a regimen involving concurrent chemoradiation followed by chemotherapy. The use of adjuvant chemotherapy in the above setting is endorsed by established clinical practice guidelines [National Comprehensive Cancer Network 2019] [Colombo, N., et al 2013]. With the widespread use of adjuvant chemotherapy, many patients with recurrent disease, who are appropriate candidates for first-line systemic treatment for advanced or recurrent disease, have received prior adjuvant chemotherapy.

In the setting of recurrent disease after prior platinum-based adjuvant chemotherapy, retreatment with paclitaxel-carboplatin chemotherapy after a platinum-free interval of >6 months results in a response rate of 50%, with a median PFS and OS after retreatment of 10 and 27 months respectively [Rubinstein, M., et al 2019]. These data approximate the efficacy for paclitaxel-carboplatin in the GOG 209 study in the first-line setting, which included a 51% response rate, and a median PFS and OS of 14 months and 32 months respectively [Miller, D., et al 2015]. Accordingly, with the inclusion of these patients, the statistical assumptions for this study, which were based on GOG 209, do not change. Therefore, it is appropriate to use carboplatin-paclitaxel for recurrent disease after prior platinum-based adjuvant chemotherapy, with the expectation of response rates comparable to those observed for chemo-naïve disease.

In summary, inclusion of participants with recurrent disease after neo/adjuvant chemotherapy is an appropriate adjustment to current practice patterns and is further justified by the high-expected efficacy of paclitaxel-carboplatin in the newly included population.

2.2.1.6 Clinical Data on Lenvatinib in Combination with Pembrolizumab for Treatment of Endometrial Carcinoma

Promising activity was observed in 53 EC participants analyzed for efficacy and safety during an interim analysis of the Phase 2 Study 111; 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 65 years, and all had an Eastern Cooperative Oncology Group (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, 8% had microsatellite instability high (MSI-H) tumors, and 8% of participants had an unknown MSI status. Thirteen participants (25%) were PD-L1 positive, 11 (21%) were PD-L1 negative, and 29 (55%) were not tested for PD-L1 status.

The best overall response (BOR) was evaluated per immune-related Response Evaluation Criteria in Solid Tumors (iRECIST) by both investigator assessment and independent radiology review. 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 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). In participants that responded, 83.0% had a DOR ≥6 months and 64.5% had a DOR ≥12 months. 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 iRECIST 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.

2.2.1.7 Clinical Data on Lenvatinib and Pembrolizumab as Single Agents for the Treatment of Endometrial Carcinoma

Eisai and the Sponsor have conducted trials 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 after 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 BICR). Per BICR, 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 AE; 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 frequently 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 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, NCT02054806). At the time of the data cutoff (17-FEB-2016), the ORR, based on RECIST 1.1 by investigator assessment, 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. Median DOR was not reached (range: 63.7+ to 64.7+ weeks) at the time of the data cutoff. 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].

The Sponsor is further investigating the clinical benefit of pembrolizumab monotherapy (200 mg administered IV Q3W) in advanced EC, irrespective of PD-L1 status, in the multi-cohort Phase 2 KEYNOTE-158 (NCT02628067) study.

As of 28-APR-2017, 107 EC participants have been treated. Most 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 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. The median DOR was not reached (range: 4.7+ to 10.0+ months) at the time of the data cutoff. 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 intervention by the investigator. Grade 3, 4, or 5 events occurred in 57.9% of participants, with 15.9% considered related to the study intervention 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 is greater than can be accounted for by each of these single agents on their own.

2.2.2 Preclinical and Clinical Studies

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

2.2.3 Ongoing Clinical Studies

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

2.2.4 Information on Other Study-related Therapy

For additional information on paclitaxel and carboplatin (or docetaxel when approved by the Sponsor due to either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel, see Section 4.3.3.1), refer to the respective approved product labels.

2.3 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 2.2.1.5 and 2.2.1.6, 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 IBs and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

In women with Stage III, Stage IV, or recurrent endometrial carcinoma who have been treated with pembrolizumab plus lenvatinib versus chemotherapy:

Objectives	**Endpoints**
Primary	
• Objective: To compare progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) by blinded independent central review (BICR), modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ (see Section 8.2.1). Hypothesis 1 (H1): The combination of pembrolizumab plus lenvatinib is superior to chemotherapy with respect to PFS per RECIST 1.1 by BICR in mismatch repair proficient (pMMR) participants. H2: The combination of pembrolizumab plus lenvatinib is superior to chemotherapy with respect to PFS per RECIST 1.1 by BICR in all-comers.	• PFS is defined as the time from randomization to first documented disease progression or death due to any cause, whichever occurs first.
• Objective: To compare overall survival (OS) H3: The combination of pembrolizumab plus lenvatinib is non-inferior to chemotherapy with respect to OS in pMMR participants. H4: The combination of pembrolizumab plus lenvatinib is superior to chemotherapy with respect to OS in pMMR participants. H5: The combination of pembrolizumab plus lenvatinib is superior to chemotherapy with respect to OS in all-comers.	• OS is defined as the time from randomization to death due to any cause.

Objectives	Endpoints
Secondary	
• Objective: To compare objective response rate (ORR) per RECIST 1.1 by BICR in pMMR participants and in all-comer participants who have measurable disease at study entry.	• Objective Response (OR) is defined as a confirmed complete response (CR) or partial response (PR).
• Objective: To evaluate the impact of treatment on Health-Related Quality-of-Life (HRQoL) as assessed by using the global score of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core-30 (QLQ-C30) in pMMR and in all-comer participants.	• Mean change from baseline in EORTC QLQ-C30 global health status/quality of life score.
• Objective: To compare the safety and tolerability of pembrolizumab plus lenvatinib versus chemotherapy in all-comer participants.	• AEs, SAEs and irAEs. • Study intervention discontinuations due to AEs.

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4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3 randomized, open-label, study of pembrolizumab plus lenvatinib (Arm 1) versus chemotherapy (Arm 2) in women at least 18 years of age with a histologically-confirmed diagnosis of Stage III, Stage IV, or recurrent endometrial carcinoma who have not previously been treated with prior systemic chemotherapy (note: prior chemotherapy administered in the adjuvant or neoadjuvant setting and/or concurrently with radiation is permitted). Participants who are candidates for curative-intent surgery should not be enrolled. Accordingly, investigators should assess the appropriateness of study participation with careful discretion.

Enrollment will be considered complete when 612 pMMR participants have been enrolled. Approximately 875 total participants are expected to be enrolled (612 pMMR participants and approximately 263 dMMR participants).

After enrollment of the global portion of the study is complete, the study may remain open to enrollment in China alone until the target number of participants in China has been enrolled to meet local regulatory requirements. An extension portion of the study will be identical to the global study, (eg, inclusion and exclusion criteria, study endpoints, primary and secondary objectives, and study procedures) and details pertaining to the statistical analyses for participants enrolled in China will be provided in a separate supplemental statistical analysis plan (sSAP).

The study includes dual-primary efficacy endpoints: 1) PFS per RECIST 1.1 as assessed by BICR and 2) OS. Eligible participants will first be stratified by MMR status (pMMR versus dMMR), then only within the pMMR stratum, participants will be further stratified according to ECOG (0 versus 1), measurable disease (yes versus no), and prior chemotherapy and/or chemoradiation (yes versus no). A total of 9 strata will be used for the study. Participants will be randomized centrally to one of 2 treatment arms:

Arm 1:
Lenvatinib 20 mg orally QD plus
Pembrolizumab 200 mg IV infusion Q3W

Arm 2:
Paclitaxel 175 mg/m^2 IV infusion Q3W plus
Carboplatin AUC 6 mg/mL/min IV infusion Q3W

A lower starting dose of paclitaxel (135 mg/m^2) and carboplatin (AUC 5 mg/mL/min) may be administered for participants who are at risk for developing toxicities due to prior pelvic/spine radiation. An AUC 5 mg/mL/min dose for carboplatin may be administered in accordance with local practice. Note: Docetaxel may be considered for participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel only after consultation with the Sponsor (see Section 4.3.3.1).

Pembrolizumab (Arm 1) and paclitaxel plus carboplatin (Arm 2) will be administered on Day 1 of each 21-day cycle. Lenvatinib (Arm 1) will be taken daily starting on Day 1 of Cycle 1.

The first on-treatment imaging assessment will be performed at 9 weeks (63 days ± 7 days) from the date of randomization. Subsequent tumor imaging should be performed Q9W (63 days ± 7 days) through Week 54 and Q12W (84 days ± 7 days) thereafter. Progressive disease will be verified by BICR per RECIST 1.1 and may be further confirmed by subsequent imaging at the site per iRECIST. Refer to Section 8.2.1 for details about tumor imaging and assessments.

Participants may receive a maximum of 35 infusions of pembrolizumab; however, in the presence of clinical benefit, lenvatinib should continue beyond 35 cycles until disease progression or unacceptable toxicity. Participants may receive up to 7 cycles of paclitaxel/carboplatin. Chemotherapy treatment beyond 7 cycles may be permitted for participants who continue to derive clinical benefit, with Sponsor approval. If needed, participants may interrupt or discontinue pembrolizumab and continue with lenvatinib;

similarly, participants may interrupt or discontinue lenvatinib and continue with pembrolizumab. This protocol does not allow participants to cross over to the pembrolizumab plus lenvatinib arm upon experiencing progression with chemotherapy.

Participants in Arm 1 who stop study intervention for reasons other than disease progression or intolerability after receiving 35 infusions of pembrolizumab or participants who attain a complete response and stop study intervention after a minimum of 8 infusions of pembrolizumab (and a minimum of 2 infusions after the complete response was attained) may be eligible for an additional 17 cycles of pembrolizumab (± lenvatinib) after experiencing disease progression; if lenvatinib is stopped due to unacceptable toxicity, it will not be restarted during second course (Second Course Phase; Section 6.6.5). Participants who discontinue pembrolizumab after receiving 35 infusions or attaining a CR should continue to receive lenvatinib alone until disease progression is verified by BICR or the development of unacceptable toxicity.

Participants who discontinue from treatment for reasons other than radiographic disease progression will have post-treatment follow-up imaging to assess disease status until disease progression is documented radiographically per RECIST 1.1 and verified by BICR (and when clinically appropriate, confirmed by the site per iRECIST), initiating a new anticancer treatment, withdrawing consent, becoming lost to follow-up, pregnancy, or death.

After verification of progression by BICR per RECIST 1.1 and/or initiation of a subsequent anticancer treatment, all participants will be followed for survival (by phone contact or clinic visit) until death, withdrawal of consent, loss to follow-up, or until the study is concluded or terminated early, whichever comes first.

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The study will have an independent eDMC to monitor safety during the course of the study, evaluate efficacy at the interim analyses, and to provide recommendations for the study in accordance with the eDMC charter and the SAP.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3 (Table 1 and Table 2). Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

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-high (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 dMMR tumors, including EC. To account for the improved efficacy of pembrolizumab in the MSI-H/dMMR 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% to 15% increase in sample size). The study will stop recruitment once fully enrolled for pMMR participants (n = 612) and it is anticipated that up to 263 dMMR participants will be enrolled. [redacted]

4.2.2 Rationale for Antidrug Antibody (ADA) Assessment

To evaluate the immunogenicity and exposure of pembrolizumab in this indication, sample collections for analysis of antidrug antibodies (ADA) were obtained, but discontinued in MK-7902-001-04. As part of the clinical development program for pembrolizumab, pre- and post-baseline serum samples from participants treated with pembrolizumab have been analyzed for ADA, and an integrated immunogenicity evaluation has been performed. Data indicates that pembrolizumab has a low potential for eliciting the formation of ADA as detailed in the pembrolizumab IB.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

This study will use PFS based on RECIST 1.1 criteria as assessed by BICR, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ and OS as dual-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 an iCRO 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 verification 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.

Objective Response is a secondary endpoint. OR 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. Images will be read per RECIST 1.1 by BICR to minimize bias in the response assessments.

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4.2.3.1.1 RECIST 1.1

RECIST 1.1 will be used by the BICR and local site when assessing images for efficacy and determining eligibility per 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 will implement a modification to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ.

4.2.3.1.2 Modified RECIST 1.1 for Immune-based Therapeutics (iRECIST)

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen after treatment with pembrolizumab (Section 8.2.1.6). Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and patients treated with pembrolizumab may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Thus, standard RECIST 1.1 may not fully capture the treatment benefits from immunotherapeutic agents such as pembrolizumab. Based on an analysis of participants with melanoma enrolled in KEYNOTE-001 (KN001), 7% of evaluable participants experienced delayed or early tumor pseudoprogression. Of note, participants who had PD by RECIST 1.1, but not by the immune-related response criteria [Wolchok, J. D., et al 2009] had longer OS than participants with PD by both criteria [Hodi, F. S., et al 2014]. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of participants. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical responses in immunotherapy and enables treatment beyond initial radiographic progression, if the participant is clinically stable.

iRECIST has been developed and published by the RECIST Working Group, with input from leading experts from industry and academia, along with the US Food and Drug Administration and the European Medicines Agency [Seymour, L., et al 2017] participation. The unidimensional measurement of target lesions, qualitative assessment of nontarget lesions, and response categories are identical to RECIST 1.1, until progression is seen by RECIST 1.1. However, if a participant is clinically stable, additional imaging will be

performed to confirm radiographic progression. iRECIST will be used by investigators to assess tumor response and progression [redacted]

4.2.3.2 Safety Endpoints

Safety parameters frequently 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 4.0.

4.2.3.3 Patient-reported Outcomes

Symptomatic improvement is considered a clinical benefit and accepted by health authorities as additional evidence of the risk-benefit profile of any new study intervention. As part of the analyses for this study, health-related quality of life (HRQoL) and disease-related symptoms will be investigated among all participants via the following assessment tools: EORTC QLQ-C30, EORTC-QLQ-EN24, and the EuroQoL EQ-5D-5L questionnaires. Health utilities will be evaluated using the EQ-5D-5L PRO instrument. PRO instruments will be administered by trained site personnel and completed electronically by participants in the following order: EORTC QLQ-C30, EORTC-QLQ-EN24, and EQ-5D-5L. These measures are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.3.3.1 EORTC QLQ-C30

EORTC QLQ-C30 is a psychometrically and clinically validated instrument appropriate for assessing HRQoL in oncology studies [Aaronson, N. K., et al 1993]. The EORTC QLQ-C30 is the most widely used cancer-specific HRQoL 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]. For the global health status or QoL and function scales, a higher value indicates a better level of function; for symptom scales and items, a higher value indicates increased severity of symptoms. Mean change from baseline in global health status or QoL scale of the EORTC QLQ-C30 will be evaluated as a secondary objective.

4.2.3.3.2 EORTC QLQ-EN24

The EORTC QLQ-EN24 is a standardized questionnaire, which permits evaluation of QoL in participants with all stages of EC managed with a specific treatment. The module consists of 24 items including 10 symptom scales (Lymphoedema, Urological and gastrointestinal symptoms, Poor body image, Sexual/vaginal problems, Pain in back and pelvis, Tingling/numbness, Muscular pain, Hair loss and taste change) and 3 functional scales (Sexual interest, Sexual activity, Sexual enjoyment).

4.2.3.3.3 EuroQoL EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in health economic analyses [Rabin, R. and de Charro, F. 2001]. The 5 health state dimensions in the EQ-5D-5L include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 5 point scale from 1 (no problem) to 5 (unable to/extreme problems). The EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the participant rates his or her general state of health at the time of the assessment. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability [Pickard, A. S., et al 2007].

4.2.3.4 Pharmacokinetic Endpoints

Based on lenvatinib PK data obtained in this study and from other studies, a population PK analysis may be performed to characterize PK parameters of lenvatinib when co-administered with pembrolizumab to support the proposed dosing regimen.

4.2.3.5 Pharmacodynamic Endpoints

No pharmacodynamic endpoints are planned for this study.

4.2.3.6 CCI

CCI

CCI

[redacted]

CCI

[redacted]

4.2.4 Rationale for the Use of Comparator

Paclitaxel and carboplatin 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 was selected based on the results of the Phase 1b portion of 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 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 + pembrolizumab 200 mg Q3W dose.

Based on review of all of the clinical data from these 13 participants, the MTD and RP2D were determined to be 20 mg lenvatinib daily in combination with a fixed dose of 200 mg pembrolizumab given Q3W.

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 every 2 weeks (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 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 (KEYNOTE-001 Cohort B2, KEYNOTE-001 Cohort D, KEYNOTE-002, KEYNOTE-010, and KEYNOTE-021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KEYNOTE-001 Cohort B3, KEYNOTE-001 Cohort F2 and KEYNOTE-006). All of these studies showed 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 dose 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 regardless 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. PK data in KEYNOTE-001 evaluating TMDD conclusively showed saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Also, 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

The doses of paclitaxel and carboplatin were selected based on standard clinical practice.

All participants should receive premedication and other supportive care measures, to prevent severe hypersensitivity reactions and minimize toxicity, according to the local label and/or per local practice.

4.3.3.1 Paclitaxel

Paclitaxel 175 mg/m^2 will be administered as an IV infusion on Day 1 of each 3-week treatment cycle according to the local label and/or per local practice.

The paclitaxel dose may be reduced to 135 mg/m^2 for participants with a history of pelvic/spine radiation.

Docetaxel may be considered for participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel only after consultation with the Sponsor. Docetaxel 75 mg/m^2 would then be administered as an IV infusion on Day 1 of each 3-week treatment cycle according to the local label and/or per local practice. Other starting doses of docetaxel should be discussed with the Sponsor.

4.3.3.2 Carboplatin

Carboplatin AUC 6 mg/mL/min will be administered as an IV infusion on Day 1 of each 3-week treatment cycle immediately after paclitaxel (or docetaxel for participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel only after consultation with the Sponsor, see Section 4.3.3.1), according to the local label and/or per local practice.

The carboplatin dose may be reduced to AUC 5 mg/mL/min for participants with a history of pelvic/spine radiation and in accordance with local practice.

4.3.4 Maximum Dose/Exposure for This Study

The maximum dose/exposure of pembrolizumab allowed in this study is 200 mg Q3W for up to 35 infusions; however, participants may be eligible for an additional 17 administrations (Section 6.6.5). Participants may receive up to 7 cycles of paclitaxel (or docetaxel for participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel only after consultation with the Sponsor, see Section 4.3.3.1) plus carboplatin. Chemotherapy treatment beyond 7 cycles may be permitted for participants who continue to derive clinical benefit, with Sponsor approval. The maximum dose/exposure of lenvatinib allowed in this study is 20 mg QD. Participants should continue treatment with lenvatinib until disease progression or unacceptable toxicity.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

Upon study completion, eligible participants may be enrolled in an extension study in which they are administered pembrolizumab monotherapy, lenvatinib monotherapy, or a

combination of both pembrolizumab and lenvatinib as received in the parent study, if available.

If the study includes countries in the EEA, the local start of the study in the EEA is defined as FSR in any Member State.

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

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 10.1.1) this study includes participants of varying age, race, and ethnicity. The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

Female participants 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

To be eligible for inclusion in this study, the participant must:

1. Have Stage III, Stage IV, or recurrent, histologically-confirmed endometrial carcinoma with disease that is either measurable or nonmeasurable per RECIST 1.1, but radiographically apparent, as assessed by BICR.

Notes about prior therapy:

- May have received 1 prior line of systemic platinum-based adjuvant and/or neoadjuvant chemotherapy in the setting of a curative-intent resection, if the recurrence occurred ≥6 months after the last dose of chemotherapy. This prior chemotherapy may be given as treatment involving chemotherapy alone, concurrent chemoradiation, or as part of a sequential approach such as in a regimen involving concurrent chemoradiation followed by chemotherapy.
- If neoadjuvant chemotherapy is used, there must be no evidence of tumor growth during this treatment prior to surgical resection.
- Instances in which both adjuvant and neoadjuvant systemic platinum-based chemotherapy are used will be counted as one line of chemotherapy.

- May have received prior radiation with or without chemotherapy (see also Section 5.2).
- May have received prior hormonal therapy for treatment of endometrial carcinoma, provided that it was discontinued ≥1 week prior to randomization.

2. Have provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion that was not previously irradiated, for determination of MMR status. *Note: FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue. If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory within 14 days from the date slides are cut (details pertaining to tumor tissue submission can be found in the Laboratory Manual).*

Demographics

3. Have an ECOG performance status of 0 or 1, as assessed within 7 days prior to the first dose of study intervention.
4. Be female and at least 18 years of age on the day of signing consent.

Female Participants

5. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

   - Is not a WOCBP

   OR

   - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 120 days post pembrolizumab or 30 days post lenvatinib, whichever occurs last, and 180 days after the last dose of chemotherapy. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.
   - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention.
   - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
   - Additional requirements for pregnancy testing during and after study intervention are in Appendix 2.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

Informed Consent

6. The participant (or legally acceptable representative if applicable) provides written informed consent for the study.

Additional Categories

7. Have adequately controlled BP with or without antihypertensive medications, defined as BP ≤150/90 mm Hg with no change in antihypertensive medications within 1 week prior to randomization.
8. Have adequate organ function as indicated by the following laboratory values (Table 3) within 7 days prior to the first dose of study intervention:

Table 3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
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]	≤3 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
INR OR PT aPTT OR 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

System	Laboratory Value
Abbreviations: ALP = alkaline phosphatase; ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCl = creatinine clearance; GFR = glomerular filtration rate; INR = International Normalized Ratio; PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal. 1. Criteria must be met without erythropoietin dependency and without pRBC transfusion within last 14 days. 2. 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 the local lab is unable to perform aPTT.	

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. Has carcinosarcoma (malignant mixed Műllerian tumor), endometrial leiomyosarcoma or other high grade sarcomas, or endometrial stromal sarcomas.
2. Participants with central nervous system (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. Has a known additional malignancy (other than endometrial carcinoma) that is progressing or has required active treatment in the last 3 years.
   Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, ductal carcinoma in situ, cervical carcinoma in situ) that have undergone potentially curative therapy are not excluded.
4. Has gastrointestinal malabsorption, or any other condition that might affect the absorption of lenvatinib.
5. Has a pre-existing Grade ≥3 gastrointestinal or nongastrointestinal fistula.
6. Has 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 after lenvatinib therapy.
7. Has active hemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks prior to the first dose of study intervention or tumor bleeding within 2 weeks prior to randomization.
8. Has clinically significant cardiovascular disease within 12 months from first dose of study intervention including New York Heart Association Class III or IV congestive heart failure, unstable angina, myocardial infarction, cerebral vascular accident, or cardiac arrhythmia associated with hemodynamic instability.

Note: Medically controlled arrhythmia is permitted.

9. Has an active infection (any infection requiring systemic treatment).
10. Has had major surgery within 3 weeks prior to first dose of study interventions. Note: Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility.
11. Has not recovered adequately from any toxicity and/or complications from major surgery prior to randomization.
12. Has a known history of human immunodeficiency virus (HIV) infection.
    Note: HIV testing is required at screening only when mandated by local health authority.
13. Has a known history of hepatitis B (defined as hepatitis B surface antigen [HBsAg] reactive) or known active hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.
    Note: Testing for Hepatitis B and Hepatitis C is required at screening only when mandated by local health authority.
14. Has a history of (noninfectious) pneumonitis that required treatment with steroids, or has current pneumonitis.
15. 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.
16. Has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the study.
17. 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 randomization.
18. Has an 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.

Prior/Concomitant Therapy

19. Has received prior systemic chemotherapy in any setting for the treatment of endometrial carcinoma (note: prior chemotherapy administered as adjuvant therapy, neoadjuvant therapy, and/or concurrently with radiation is permitted).
20. Has received prior radiotherapy within 4 weeks prior to randomization. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 2-week washout is permitted for palliative radiation to non-CNS disease and vaginal brachytherapy.

21. Has received prior hormonal therapy for the treatment of endometrial carcinoma within 1 week of randomization.
22. Has received prior therapy with any treatment targeting VEGF-directed angiogenesis, an anti-PD-1, anti-PD-L1, or anti-PD L2 agent, or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX 40, CD137).
23. Has received a live or live attenuated vaccine within 30 days prior to the first dose of study intervention. Note: Administration of killed vaccines is allowed.
24. Has known intolerance to study intervention (or any of the excipients).
25. Has had an allogenic tissue/solid organ transplant.

Prior/Concurrent Clinical Study Experience

26. 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 randomization.

    Note: Participants who have entered the Follow-up Phase of an investigational study may participate as long as it has been ≥4 weeks from the last dose of the investigational agent and randomization.

Diagnostic Assessments

27. Has urine protein ≥1 g/24 hours.

    Note: Participants with proteinuria ≥2+ (≥100 mg/dL) on urine dipstick testing (urinalysis) will undergo 24-hr urine collection for quantitative assessment of proteinuria.

28. Has prolongation of QTcF interval to >480 ms (corrected by Fridericia Formula).
    Note: If the QTcF is prolonged to >480 ms in the presence of a pacemaker, contact the Sponsor to determine eligibility.

29. Has left ventricular ejection fraction (LVEF) below the institutional normal range as determined by multigated acquisition (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

Based on its mechanism of action, lenvatinib can cause fetal harm when administered to a pregnant woman. Lenvatinib may also result in reduced fertility in females of reproductive potential and may result in damage to male reproductive tissues leading to reduced fertility of unknown duration. In animal reproduction studies, oral administration of lenvatinib during

organogenesis at doses below the recommended human dose resulted in embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits.

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. To participate in the study, participants of childbearing potential must adhere to the contraception requirement (Appendix 5) from the day of study medication initiation throughout the study period up to 120 days after the last dose of pembrolizumab or 30 days post the last dose of lenvatinib, whichever comes last, and 180 days after the last dose of chemotherapy. 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 intervention, the participant will be immediately discontinued from study intervention. 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 the Sponsor 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 the Sponsor as described in Section 8.4.1.

5.3.4 Use in Nursing Women

It is unknown whether the study interventions 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 in the study. 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 AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention OR withdraws from the study will not be replaced.

6 STUDY INTERVENTION

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

"Study intervention" refers to pembrolizumab, lenvatinib, paclitaxel (or docetaxel for participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel only after consultation with the Sponsor, see Section 4.3.3.1) and/or carboplatin.

Clinical supplies will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 4.

Table 4 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)[a]	Dosage Level(s)[b, e]	Route of Administration	Regimen/ Treatment Period	Use	IMP or NIMP/AxMP[f]	Sourcing[c, d]
Arm 1	Experimental	Lenvatinib	Drug	Capsule	10 mg, 4 mg	20 mg	Oral	Once daily	Test Product	IMP	Central
Arm 1	Experimental	Pembrolizumab	Drug	Vial	25 mg/mL	200 mg	IV Infusion	Day 1 of each cycle	Test Product	IMP	Central
Arm 2	Active Comparator	Paclitaxel	Drug	Vial	6 mg/mL (16.7 mL)	175 mg/ m^2	IV Infusion	Day 1 of each cycle	Comparator	IMP	Local or Central
Arm 2	Active Comparator	Carboplatin	Drug	Vial	10 mg/mL (60 mL)	AUC 6 mg/ mL/min	IV Infusion	Day 1 of each cycle	Comparator	IMP	Local or Central

a. Unit dose strength and volume may vary depending on market availability.

b. Paclitaxel 175 mg/m^2 IV infusion Q3W; carboplatin AUC 6 mg/mL/min IV infusion Q3W. Docetaxel may be considered for participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel only after consultation with the Sponsor (see Section 4.3.3.1).

c. 4 mg capsules provided for successive dose reduction of lenvatinib, if needed, as described in Section 6.6.1.

d. Paclitaxel (or docetaxel for participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel only after consultation with the Sponsor, see Section 4.3.3.1) and carboplatin should be provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee. Pembrolizumab and lenvatinib should be provided centrally by the Sponsor.

e. A lower starting dose of paclitaxel (135 mg/m^2) and carboplatin (AUC 5 mg/mL/min) may be administered for participants who are at risk for developing toxicities due to prior pelvic/spine radiation. An AUC 5 mg/mL/min dose for carboplatin may be administered in accordance with local practice.

f. The definition of IMP and NIMP/(AxMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP or NIMP/AxMP may exist. In these circumstances, local legislation is followed.

All study interventions will be administered on an outpatient basis.

All supplies indicated in Table 4 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, 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 intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual. Lenvatinib is a capsule for oral administration and does not require preparation. Paclitaxel and carboplatin (or docetaxel if used in place of paclitaxel for participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel only after consultation with the Sponsor, see Section 4.3.3.1) should be prepared as outlined in the respective approved labeling or institutional guidelines.

6.2.2 Handling, Storage, and Accountability

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

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions 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 intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor 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 the Sponsor.

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 interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Treatment allocation/randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to lenvatinib + pembrolizumab study intervention and paclitaxel + carboplatin study intervention, respectively.

6.3.2 Stratification

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

- MMR status (pMMR versus dMMR), and if pMMR:
  - ECOG (0 versus 1)
  - Measurable disease (yes versus no)
  - Prior chemotherapy and/or chemoradiation (yes versus no)

Eligible participants will first be stratified by MMR status (pMMR versus dMMR), then only within the pMMR stratum, participants will be further stratified according to ECOG (0 versus 1), measurable disease (yes versus no), and prior chemotherapy and/or chemoradiation (yes versus no). A total of 9 strata will be used for the study.

6.3.3 Blinding

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

6.4 Study Intervention Compliance

If there are interruptions in the study intervention schedule, the details of and reason for any interruption of study intervention will be documented in the participant's medical record.

Refer to Section 6.6.1 for dose modifications and toxicity management for lenvatinib and to Section 6.6.2 for dose modification and toxicity management for irAEs associated with pembrolizumab and for other allowed dose interruption of pembrolizumab. Refer to Section 6.6.3 for dose modifications management for overlapping toxicities.

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 intervention may be required. The

investigator is to discuss prohibited medication with the Sponsor's 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 intervention requires the mutual agreement of the investigator, 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 intervention 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 intervention 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 antidiarrheal 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 definitively treated breast cancer.
- Anticoagulants including low molecular weight heparin, 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 of up to 2 pre-existing, nontarget bone metastases will be permitted. Palliative radiotherapy of other nontarget lesions may be permitted after consultation with the Sponsor.

Any additional procedural or participant-specific particularities should be discussed with the Sponsor.

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 (eg, 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.
- Immunotherapy not specified in this protocol.
- Investigational agents other than pembrolizumab, lenvatinib, paclitaxel (or docetaxel for participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel, only after consultation with the Sponsor, see Section 4.3.3.1), and carboplatin.
- Live or live attenuated vaccines within 30 days prior to the first dose of study intervention and while participating in the study. Killed vaccines are allowed.
- For participants in the lenvatinib plus pembrolizumab arm, systemic glucocorticoids are not permitted except 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 >10 mg/day prednisone equivalent for COPD exacerbations.
  - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent.
- In addition, the following nonsystemic 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 on with the Sponsor.

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. All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in

keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF including all prescription, OTC products, herbal supplements, IV medications, and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 28 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. All concomitant medications administered during SAEs or ECIs are to be recorded. SAEs and ECIs are defined in Section 8.4.

For further information on the prohibited concomitant therapies for paclitaxel or carboplatin (or docetaxel for participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel only after consultation with the Sponsor, see Section 4.3.3.1), please refer to their respective prescribing information.

6.5.3 Drug-Drug Interactions

A clinical drug-drug interaction (DDI) study in cancer patients showed that plasma concentrations of midazolam (a sensitive CYP3A and Pgp substrate) were not altered in a clinically meaningful manner in the presence of lenvatinib. No significant drug-drug interaction is therefore expected between lenvatinib and other CYP3A4/Pgp substrates.

Nonclinical studies identify CYP3A4 as the important CYP isozyme responsible for human hepatic metabolism of lenvatinib. However, clinical studies conducted showed that co-administration of lenvatinib with either inducers or inhibitors of CYP3A4/P-glycoprotein (Pgp) are not of clinical concern.

There are no DDI-related concomitant medication prohibitions or restrictions. Lenvatinib is not expected to clinically meaningfully alter exposure to CYP3A4/ P-glycoprotein (Pgp) substrates based on results from a lenvatinib DDI study with midazolam (a sensitive CYP3A and Pgp substrate). Clinical studies also showed that co-administration of lenvatinib with either inducers or inhibitors of CYP3A4/Pgp are not of clinical concern. No drug interaction is expected between pembrolizumab and lenvatinib because of 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 nonenzymatic 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.

For participants receiving pembrolizumab + lenvatinib, suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined in Table 6, Section 6.6.2.1, along with the dose modification guidelines in Table 5, in Section 6.6.1.

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 6 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)

6.6.1 Lenvatinib Dose Modification

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 5. An interruption of study intervention for more than 28 days will require Sponsor approval before treatment can be resumed.

Adverse events will be graded using NCI CTCAE Version 4.0. 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.

The starting dose of lenvatinib is 20 mg/day for participants enrolled in Arm 1. 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 the Sponsor. 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, the Sponsor'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), PRES/RPLS (Section 6.6.1.6), hypocalcemia (Section 6.6.1.7), hemorrhage (Section 6.6.1.8), gastrointestinal perforation or fistula formation (Section 6.6.1.9), QT prolongation (Section 6.6.1.10) , and osteonecrosis of the jaw (Section 6.6.1.11) as appropriate, before consulting the dose modification table (Table 5). For overlapping toxicities of pembrolizumab and lenvatinib, please refer to Section 6.6.3.

Table 5 Dose Modification Guidelines for Lenvatinib-related Adverse Events (for the Lenvatinib-Pembrolizumab Combination)

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,g]		
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 Sponsor
Grade 4[f]: Discontinue Study Treatment		

Abbreviations: AE = adverse event; BMI = body mass index; CTCAE = Common Terminology Criteria for Adverse Events.

Note: For grading see CTCAE version 4.0. Collect all AE grades (ie, decreasing and increasing CTCAE grade).

a. An interruption of study treatment for more than 28 days will require Sponsor 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 their baseline weight or within 10% of their baseline weight (ie, Grade 1 weight loss). These participants may restart study intervention at a lower dose once their weight remains stable for at least 1 week and they reach at least a 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 should be discussed with Sponsor.
f. Excluding laboratory abnormalities judged to be nonlife-threatening, in which case manage as Grade 3.
g. For Grade 3 thromboembolic event, permanently discontinue lenvatinib. See Section 6.6.1.5.

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 v4.0, based on BP measurements only (and not on the number of antihypertensive medications).

If the participant's initial BP measurement 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 significant risk factors for severe complications of uncontrolled hypertension (eg, BP ≥160/100 mm Hg, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant comorbidities). 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.

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 intervention 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 intervention 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 the Sponsor.

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

1. Institute appropriate medical management
2. Discontinue study intervention

6.6.1.2 Management of Proteinuria

Regular assessment of proteinuria should be conducted as detailed in the SoA (Section 1.3.1 and Section 1.3.2). Guidelines for assessment and management of proteinuria are as follows:

Detection and Confirmation

1. Perform urine dipstick testing or urinalysis per the SoA (Section 1.3.1 and 1.3.2). Urine dipstick testing is the preferred method for testing for urinary protein; however, urinalysis may be used if the use of urine dipsticks is not feasible.
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+ (≥100 mg/dL) proteinuria on urine dipstick (or urinalysis) while on study intervention.
   - A subsequent increase in severity of urine dipstick or urinalysis 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+ (≥100 mg/dL).
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

1. Grading according to NCI CTCAE v4.0 will be based on the 24-hour urinary protein result if one has been obtained. If the participant has 4+ proteinuria by dipstick (≥1000 mg/dL by urinalysis), a 24-hour urinary protein result is required to confirm Grade 3 proteinuria. Management of lenvatinib administration will be based on the grade of proteinuria according to Table 5.

Monitoring

a. Urine dipstick or urinalysis testing for participants with proteinuria ≥2+ (≥100 mg/dL) should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ (30 mg/dL) or negative for 2 consecutive treatment cycles.

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

c. In the event of nephrotic syndrome, lenvatinib must be discontinued.

6.6.1.3 Management of Diarrhea

An antidiarrheal agent should be recommended to the participant at the start of study intervention and participants should be instructed and educated to initiate antidiarrheal treatment at the first onset of soft bowel movements. The choice of antidiarrheal 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 5 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 5 should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure (any grade per CTCAE v4) occurs, lenvatinib 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 that 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. If 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 5 should be followed. Appropriate supportive care should be provided together with close monitoring. If a

participant experiences a Grade 3 or a life-threatening (Grade 4) thromboembolic reaction, 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 intervention 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 5 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 v4.0, 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 5 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 Grade 4 fistula.

6.6.1.10 Management of QT Prolongation

Lenvatinib should be withheld in the event of development of QT interval prolongation greater than 500 msec. Lenvatinib should be resumed at a reduced dose when QTc

prolongation is resolved to <480 msec or baseline. Monitor potassium, calcium and magnesium, and replenish as appropriate.

6.6.1.11 Management of Osteonecrosis of the Jaw

Perform an oral examination prior to treatment with lenvatinib and periodically during lenvatinib treatment. Advise participants regarding good oral hygiene practices. Avoid invasive dental procedures, if possible, while on lenvatinib treatment, particularly in participants at higher risk. For participants requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ. Withhold lenvatinib if ONJ develops and restart based on clinical judgement of adequate resolution (See Section 6.6.4).

6.6.2 Pembrolizumab Dose Modification

6.6.2.1 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)

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 6.

Table 6 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 7.

Table 7 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 intervention.	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 to 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 after 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 intervention.	No subsequent dosing.
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 v4.0 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 intervention. Therefore, evaluation of attribution is important for determining the study intervention 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, T1DM) and other supportive care should be taken promptly.

Participants receiving the combination therapy (pembrolizumab + lenvatinib) must discontinue study therapy if any of the following occur:

- ALT or AST >5 X ULN for more than 2 weeks

  Pembrolizumab will have already been permanently discontinued per Table 6, 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 X ULN and (TBL >2 X ULN or INR >1.5)
  Although Table 6 advises pembrolizumab to be withheld (interrupted), and Table 5 advises lenvatinib to have no dose modification or a reduction, if this criterion is met, both drugs must be permanently discontinued immediately.

- ALT or AST >3 X ULN with appearance of at least 1 of the following: fatigue, nausea, vomiting, RUQ pain/tenderness, fever, rash, and/or eosinophilia (>5%).
  Although Table 6 advises pembrolizumab to be withheld (interrupted), and Table 5 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

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 2 weeks 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 and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 3 weeks (21 days) of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for interruption is to be documented in the participant's study record.

Pembrolizumab may be interrupted for treatment-related AEs for up to 12 weeks. Resuming pembrolizumab after an interruption >12 weeks requires Sponsor consultation.

Resuming lenvatinib after an interruption from the protocol-specified treatment plan for >28 consecutive days requires Sponsor consultation.

Resuming paclitaxel (or docetaxel for participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel only after consultation with the Sponsor, see Section 4.3.3.1)/carboplatin after an interruption from the protocol-specified treatment plan for >6 weeks requires Sponsor consultation.

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) with or without 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:

- 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 intervention, 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.

AND EITHER

- Stopped initial treatment with pembrolizumab with or without stopping of lenvatinib, after attaining an investigator-determined confirmed CR according to RECIST 1.1.
  - Was treated for at least 8 infusions of pembrolizumab before discontinuing therapy, and
  - Received at least 2 infusions of pembrolizumab beyond the date when the initial CR was declared.

OR

- Had SD, PR or CR and stopped pembrolizumab treatment after completion of 35 infusions (approximately 2 years) of study intervention for reasons other than disease progression or intolerability.

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.

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

6.6.6 Paclitaxel and Carboplatin Chemotherapy

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

Prophylactic use of granulocyte colony stimulating factors may be used to treat treatment-emergent neutropenia per local guidelines.

For participants who have transitioned to docetaxel due to a severe hypersensitivity reaction or an AE requiring discontinuation of paclitaxel (after Sponsor consultation), management of the docetaxel-related toxicity will be in accordance with the respective docetaxel prescribing information in each country/region or local institutional guidelines (see Section 4.3.3.1).

6.7 Intervention After the End of the Study

Upon study completion, participants are to be discontinued and may be enrolled in an extension study in which they are administered pembrolizumab monotherapy, lenvatinib monotherapy, or a combination of both pembrolizumab and lenvatinib as received in the parent study, if available.

6.8 Clinical Supplies Disclosure

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention 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 intervention. Therefore, all participants who discontinue study intervention 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 8.11.3.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.9 and Section 8.11.3.

A participant must be discontinued from study intervention 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 intervention.

- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Confirmed radiographic disease progression (iCPD) outlined in Section 8.2.1.6 (exception if after obtaining informed consent addendum and Sponsor communication, the investigator may elect to continue treatment beyond confirmed disease progression).
- Any progression or recurrence of any malignancy, or occurrence of another malignancy that requires active treatment.
- Unacceptable toxicity as described in Section 6.6 and Table 5 and Table 6.
- ALT or AST elevation meeting the following criteria:
  - ALT or AST >5 X ULN for more than 2 weeks

    Pembrolizumab will have already been permanently discontinued per Table 6, 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 X ULN and (TBL >2 X ULN or INR >1.5)

    Although Table 6 advises pembrolizumab to be withheld (interrupted), and Table 5 advises lenvatinib to have no dose modification or a reduction, if this criterion is met, both drugs must be permanently discontinued immediately.

  - ALT or AST >3 X ULN with appearance of at least 1 of the following: fatigue, nausea, vomiting, right upper quadrant (RUQ) pain/tenderness, fever, rash, and/or eosinophilia (>5%)

    Although Table 6 advises pembrolizumab to be withheld (interrupted), and Table 5 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.
- The study is terminated by the Sponsor.
- The study is terminated by the local health authority, IRB, or IEC.
- Completion of 35 infusions of pembrolizumab or up to 7 cycles of paclitaxel (or docetaxel for participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel only after consultation with the Sponsor, see Section 4.3.3.1) plus carboplatin. *Note: If a participant in Arm 1 completes 35 infusions of pembrolizumab, she should continue with lenvatinib alone until disease progression or unacceptable toxicity*.

7.2 Participant Withdrawal From the Study

It has been well-documented that a higher rate of withdrawal can render a study uninterpretable; therefore, unnecessary withdrawal of participants should be avoided.

As clinical event data are important study endpoints, participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue all remaining study visits for follow-up and vital status assessment as outlined in the SoA and Section 8.11.3.

The investigator is to inform the participants that:

- They may discontinue from study intervention at any time during the study, and
- They are encouraged to continue visits in the study for follow-up, imaging, and vital status assessment

If participants elect to stop study procedures, they are encouraged to continue to be followed, which allows periodic survival follow-up and vital status data to be collected.

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 ensuring 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 study-related medical or dental decisions must be made by an investigator who is a qualified physician.
- 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 the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), 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 medically qualified designee (consistent with local requirements) 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 medically qualified designee must ensure the appropriate consent is in place.

Rescreened participants do not need to be reconsented if original consent was obtained greater than 28 days prior to Cycle 1.

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.

The participant or legally acceptable representative will be asked to sign consent at the point of initial radiographic disease progression if the investigator recommends continuation of study intervention.

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 Sponsor requirements.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator who is a qualified physician to ensure that the participant qualifies for the study.

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 used 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 intervention 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 healthcare provider can obtain information about study intervention 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 important.

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 International Federation of Gynecology and Obstetrics (FIGO) stage at initial diagnosis (see Appendix 9), histopathology, location(s) of tumor burden, and all prior treatment (including prior radiation, prior chemotherapy, and prior surgery).

Participants will have disease that is either measurable or nonmeasurable per RECIST 1.1, but radiographically apparent, as assessed by BICR and defined in the 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 28 days before first dose of study intervention.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study. This also includes new medications started during the Second Course Phase through the Second Course Safety Follow-up Visit.

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 1 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/rescreening) are provided in Section 8.11.1.

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 Study Intervention Administration

Study interventions 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 and Day 15 of Cycle 1 and Day 1 of Cycle 2. Please refer to Section 8.1.8.1.1 for further detail.

Study intervention 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.

Participants will be instructed to bring their lenvatinib bottles with them to each study visit. Drug accountability should be evaluated and documented by site personnel, and appropriate steps should be taken to optimize compliance, if needed. 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 Chemotherapy

Chemotherapy consists of paclitaxel (or docetaxel for participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel only after consultation with the Sponsor, see Section 4.3.3.1) plus carboplatin.

Paclitaxel will be administered IV as a 1-hour infusion (or per institutional guidelines) at a dose of 175 mg/m^2 administered on Day 1 of each 21-day cycle.

Carboplatin will be administered IV as a 1-hour infusion (or per institutional guidelines) at AUC 6 mg/mL/min on Day 1 of each 21-day cycle.

A lower starting dose of paclitaxel (135 mg/m^2) and carboplatin (AUC 5 mg/mL/min) may be administered for participants who are at risk for developing toxicities due to prior pelvic/spine radiation. An AUC 5 mg/mL/min dose for carboplatin may be administered in accordance with local practice.

The administration procedure should follow the approved prescribing information for paclitaxel or carboplatin (or docetaxel for participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel only after consultation with the Sponsor, see Section 4.3.3.1) in each country/region or institutional guidelines.

8.1.9 Discontinuation and Withdrawal

Participants who withdraw consent from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal.

If discontinuation occurs ≥30 days after the last dose of study treatment, a Safety Follow-up Visit (Section 8.11.3.1) 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.

8.2 Efficacy/Immunogenicity Assessments

8.2.1 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the iCRO 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 necessary 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 to confirm radiographically apparent disease will be assessed by BICR. For stratification prior to randomization, measurable disease (yes versus no) will be assessed by BICR per RECIST 1.1. Participants with fluid-only disease (eg, pleural effusion or ascites, and no other radiographically apparent lesions), must have cytologic confirmation of malignancy.

All scheduled images for all study participants from the sites will be submitted to the central imaging vendor. 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 demonstrates radiologic progression, should also be submitted to the central imaging vendor.

Sites will follow RECIST 1.1 to assess response and progression.

When the investigator identifies radiographic progression per RECIST 1.1, the central imaging vendor will perform expedited verification of radiologic PD and communicate the results to the study site and Sponsor (see Section 8.2.1.5 and Figure 2). Treatment should continue until PD has been verified. Regardless of whether PD is verified, if the investigator considers the participant has progressed, but elects to implement iRECIST, the investigator will assess for confirmation of progression by iRECIST at subsequent time points. Images should continue to be submitted to the central imaging vendor.

8.2.1.1 Initial Tumor Imaging

The screening images must be submitted to the central imaging vendor for prospective review.

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 central imaging vendor.

Bone scans performed as part of routine clinical management are acceptable for use as screening imaging if they are of diagnostic quality and performed within 42 days prior to the date of randomization and can be assessed by the central imaging vendor.

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 9 weeks (63 days ±7 days]) from the date of randomization. Subsequent tumor imaging should be performed every 9 weeks (63 days ±7 days) or more frequently if clinically indicated. After 54 weeks (378

days ±7 days]), participants who remain on treatment will have imaging performed every 12 weeks (84 days ±7 days). Imaging timing should follow calendar days 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 central imaging vendor (unless the investigator elects to continue treatment and follow iRECIST), the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first. All supplemental imaging must be submitted to the central imaging vendor.

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 central imaging vendor.

Per iRECIST (Section 8.2.1.6), disease progression should be confirmed by the site 4 to 8 weeks after central verification of site-assessed first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed by the site provided they have met the conditions detailed in Section 8.2.1.6. Participants who receive confirmatory imaging 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, if clinically stable. Participants who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study intervention. Exceptions are detailed in Section 8.2.1.6.

8.2.1.2.1 Bone Imaging During the Study

A bone scan 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 42 days prior to randomization (historical is acceptable). Subsequent bone scans in these participants with bone metastases at baseline will be performed at W27, and W54 after randomization, and every 24 weeks (±7 days) thereafter, or as clinically indicated, and ≤2 weeks after a CR as assessed by the investigator.

8.2.1.2.2 Brain Imaging During the Study

A brain scan at screening will only be performed in participants who have a history of protocol-eligible brain metastases or are clinically symptomatic. The screening brain scan should be performed within 28 days prior to randomization. Subsequent brain scans in these participants with brain metastases at baseline will be performed every 9 weeks (±7 days) after randomization through W54 and Q12W thereafter, or as clinically indicated thereafter, and ≤2 weeks after 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 intervention, 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 intervention due to documented disease progression, this is the final required tumor imaging if the investigator elects not to implement iRECIST.

For participants who discontinue study intervention 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 (every 9 or 12 weeks) 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 iCRO 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. Participants who remain on treatment will have imaging performed as determined by the treating physician per the local standard of care, but not less frequently than every 12 weeks (84 days ±7 days).

Per iRECIST (Section 8.2.1.6), if tumor imaging shows initial PD, tumor assessment should be repeated 4 to 8 weeks later to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. Participants who obtain confirmatory imaging do not need to undergo scheduled tumor imaging if it is less than 4 weeks later and may wait until the next scheduled imaging time point, if clinically stable.

Imaging should continue to be performed until disease progression, the start of a new anticancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. In clinically stable participants, disease progression may be confirmed by the investigator using iRECIST 4 to 8 weeks after the first tumor imaging indicating PD.

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

For participants who discontinue Second Course study intervention 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 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 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 12 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 intervention). 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.

Investigator-assessed scans are to be submitted immediately to the iCRO for BICR verification of progression. After submission of scans, the iCRO will email the assessment to the site and Sponsor.

If disease progression is not verified, the process continues as follows:

- If participant is clinically stable, continue study intervention per protocol at investigator discretion
  - resume imaging per protocol schedule (≥4 weeks to next scan)
  - send scans to iCRO
  - continue local assessment
  - do not change investigator assessment of progression
  - if subsequent scan(s) indicate progression, submit scan(s) to iCRO to request verification
- If the participant is not clinically stable, best medical practice is to be applied

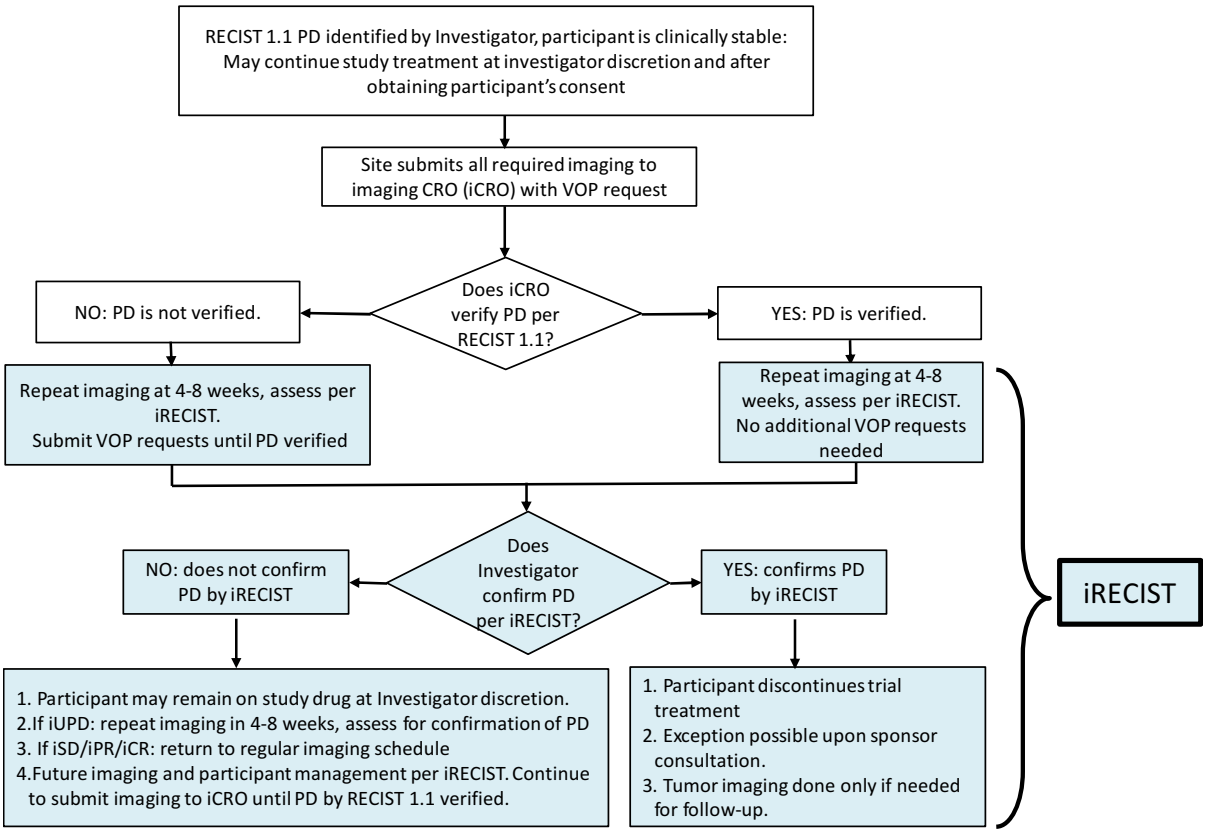
If disease progression is verified, the process continues as follows:

- Investigator judgment will determine action
- If the participant is clinically stable and study intervention is to continue, a reconsent addendum must be signed
- Obtain scans locally per original protocol schedule
- Do not send scans to iCRO

Figure 2 illustrates the study intervention decision process involving verification of disease progression for participants.

- For the purpose of this decision process, lack of clinical stability is defined as:
  - unacceptable toxicity
  - clinical signs or symptoms indicating clinically significant disease progression
  - decline in performance status
  - rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention

Figure 2 Imaging and Treatment for Clinically Stable Participants After First Radiologic Evidence of PD Assessed by the Investigator



Abbreviations: iCR=immune-related complete response; iCRO=imaging contract research organization; iPR=immune-related partial response; iRECIST=Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iUPD=immune-related unconfirmed progressive disease; PD=progressive disease; RECIST=Response Evaluation Criteria in Solid Tumors.

8.2.1.6 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression, and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules outlined in Appendix 8. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease.
- No decline in ECOG performance status.

- No requirements for intensified management, including increased analgesia, radiation, or other palliative care.

Any participant deemed clinically unstable should be discontinued from study intervention at central verification of site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the investigator decides to continue treatment, the participant may continue to receive study intervention and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment. Images should continue to be sent in to the central imaging vendor for potential retrospective BICR.

If repeat imaging does not confirm PD per iRECIST, as assessed by the investigator, and the participant continues to be clinically stable, study intervention may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study intervention.

If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 8, study intervention should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study intervention may be considered after consultation with the Sponsor. In this case, if study intervention is continued, tumor imaging should continue to be performed after the intervals as outlined in Section1.3 and submitted to the central imaging vendor.

A description of the adaptations and iRECIST process is provided in Appendix 8, with additional details in the iRECIST publication [Seymour, L., et al 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 8 and illustrated as a flowchart in Figure 2.

Table 8 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1 per investigator assessment	Submit the imaging to BICR for verification. Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the assessment of the investigator and after the participant's consent.	Submit the imaging to BICR for verification. Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment
First radiologic evidence of PD by RECIST 1.1 which has been verified by the central imaging vendor	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study intervention at the investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
Repeat tumor imaging confirms PD (iCPD) by iRECIST per investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study intervention at the investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.

Abbreviations: BICR = blinded independent central review; iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iPR = iRECIST partial response; iRECIST = Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1; VOP = verification of progression

Note: If progression has been centrally verified, further management is by the site, based on iRECIST. Any further imaging should still be submitted to the iCRO, but no rapid review will occur. If RECIST 1.1 disease progression has not been centrally verified, the site should continue treatment. Whether treatment continues, imaging should be collected and submitted to the iCRO with VOP request until RECIST 1.1 progression is verified by BICR.

8.2.2 Patient-reported Outcomes

The EORTC QLQ-C30, EORTC QLQ-EN24, and EQ-5D-5L, questionnaires will be administered by trained site personnel and completed electronically by participants in the following order: 1) EORTC QLQ-C30, 2) EORTC QLQ-EN24, then 3) EuroQoL EQ-5D-5L. HRQoL will be assessed at on Day 1 of every cycle through Cycle 35, then every 4 cycles through Cycle 60, at time of discontinuation, at the 30 day and 90 day Safety Follow-up visit.

It is best practice and strongly recommended that electronic patient-reported outcomes (ePROs) are administered to randomized participants prior to drug administration, AE evaluation, and disease status notification. If the participant does not complete the ePROs at a scheduled time point, the MISS_MODE form must be completed to capture the reason the assessment was not performed.

NOTE: For some sites, the translated EORTC QLQ-C30 and/or EORTC QLQ-EN24 might become available after study startup and should be administered to participants at their time of enrollment; for some sites, the EORTC QLQ-C30 and/or EORTC QLQ-EN24 translation might not be available for the entire duration of the study.

NOTE: If at the time of enrollment of a participant, the translated version of the EORTC QLQ EN24 is not available for that language/country, and therefore cannot be completed by the participant at Cycle 1 Day 1, then the EORTC QLQ-EN24 will not be required for this participant at any point during the study. The other study PRO measures must be completed as scheduled.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood to be drawn/collected over the course of the study, including approximate blood volume drawn/collected by visit and by sample type per participant, can be found in the Procedures Manual.

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

8.3.1 Physical Examinations

Physical examinations including oral examination (comprehensive or symptom-directed) will be performed as specified in the SoA (Section 1.3.1 and Section 1.3.2). A comprehensive physical examination will include evaluations of the head, eyes, ears, mouth, 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], heart rate [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.
- BP 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 BP <90 mm Hg. If the participant's initial BP measurement 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, for Day 15 blood pressure monitoring (Cycle 3 onwards, if applicable), participants will have the option of having BP measured between visits 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.

See Section 10.7, Appendix 7 for Country-specific Requirements.

8.3.3 Electrocardiograms

- Electrocardiograms (ECGs) will be obtained as designated in the SoA (Section 1.3). 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.
- QTc prolongation has been seen in some lenvatinib studies. Monitor ECGs every cycle (as specified in the Schedule of Assessments) 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. Please refer to the lenvatinib IB.
- 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.

8.3.4 Echocardiogram or Multiple Gated Acquisition Scan

A MUGA scan (using technetium-based tracer) or an ECHO will be performed to assess LVEF as designated in the SoA (Section 1.3). MUGA or eECHO 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 on institutional reports.

8.3.5 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) 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 2, 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 intervention, 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.

8.4 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 8.4.6 and Appendix 3.

Adverse events, 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 and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

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 intervention allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause 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 intervention allocation/randomization through 90 days, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation/randomization through 120 days after cessation of study intervention or 30 days after cessation of study intervention 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 intervention allocation/randomization through 120 days after cessation of study intervention, or 30 days after cessation of study intervention 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 the time period specified above must be reported immediately to the Sponsor if the event is considered drug-related.

Investigators are not obligated to actively seek AEs or SAEs 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 intervention or study participation, the investigator must promptly notify the Sponsor.

Participants who Enter the Extension Study:

From the time of intervention randomization up to the signing of consent to the extension study, all AEs, SAEs, and other reportable safety events must be reported by the investigator in this protocol (parent study). Laboratory values that meet criteria for reporting as AEs performed during the parent study will be collected in the parent study.

Note: Once consented to the extension study, safety events, including those considered related to study intervention, will be collected as instructed in the extension study.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 9.

Table 9 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
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
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: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential DILI - require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (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

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

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

Care will be taken not to introduce bias when detecting AEs and/or SAEs 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 AEs, SAEs, 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 the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor 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 the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 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 the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, 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.

8.4.6 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 the Sponsor 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 will ensure that unblinded aggregated efficacy endpoint events and safety data are monitored to safeguard the participants in the study.

8.4.7 Events of Clinical Interest (ECIs)

Selected nonserious and SAEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

- An overdose of Sponsor's product, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.
- 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 Study File Binder (or equivalent).

8.5 Treatment of Overdose

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

- Pembrolizumab: ≥5 times the protocol-specified dose.
- lenvatinib: any dose above the protocol-prescribed dose if associated with an adverse event
- chemotherapy: any dose ≥20% over the prescribed dose described in the protocol

In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. 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 participants 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 and RCC.

No specific information is available on the treatment of overdose of pembrolizumab, lenvatinib or chemotherapy. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

All reports of pembrolizumab overdose with and without an AE and all reports of lenvatinib overdose with an AE must be reported by the investigator within 24 hours to the Sponsor, either by electronic media or paper. 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”.

8.6 Pharmacokinetics

To evaluate the immunogenicity and exposure of pembrolizumab in this indication, sample collections for analysis of ADA and PK were obtained, but are discontinued in MK-7902-001-04. Blood samples for PK and ADA collected may be stored only at this time. Further analysis may be performed if required and reported separately if conducted.

To evaluate the exposure of lenvatinib in combination with pembrolizumab, blood samples were collected from all participants, but are discontinued in Amendment 4.

Plasma concentrations of lenvatinib when co-administered with pembrolizumab may be measured. If performed, lenvatinib will be quantified by use of validated High Performance Liquid Chromatography-tandem mass spectroscopy method and data will be analyzed using a population PK approach.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Mismatch Repair

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.

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 the Sponsor as long as all other screening procedures are performed within the correct timeframe.

8.9 CCI [redacted]

CCI [redacted]

8.9.1 Planned Genetic Analysis Sample Collection

Samples should be collected for planned analysis of associations between genetic variants in germline/tumor DNA and drug response. If a documented law or regulation prohibits (or local IRB/Independent Ethics Committee [IEC] does not approve) sample collection for these purposes, then such samples should not be collected at the corresponding sites.

If providing slides, it is requested that the remainder of the tissue block be maintained at the site until the end of the study if a bridging study is required for development of the MMR assay.

8.10 Health Economics Medical Resource Utilization and Health Economics

CCI [redacted]

8.11 Visit Requirements

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

8.11.1 Screening

Approximately 28 days prior to intervention allocation/randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Screening procedures may be repeated after consultation with the Sponsor.

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:

- 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 performed 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 the Sponsor.
- Evaluation of ECOG is to be performed within 7 days prior to the date of first dose of study treatment.
- For women of reproductive potential, a urine or serum pregnancy test will be performed prior to randomization and within 24 hours prior to first dose of study intervention. If less than 24 hours have elapsed between the randomization test and first dose a second test is not required. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local trial site laboratory).
- Newly or recently obtained tumor tissue must have been obtained prior to randomization and preferably after the latest systemic treatment for EC.

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. Rescreened participants do not need to be reconsented if original consent was obtained greater than 28 days prior to Cycle 1.

8.11.2 Treatment Period

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

8.11.3 Post-treatment Visit

8.11.3.1 Safety Follow-up

Safety Follow-up will occur during 2 separate visits: 30 days and 90 days after last dose. One mandatory Safety Follow-up visit should be conducted approximately 30 days after the last dose of study intervention or before the initiation of a new anticancer treatment, whichever comes first.

The 90-day Safety Follow-up visit is only required for participants who have not yet started new anticancer treatment. If the 90-day Safety Follow-up visit falls within the same window as an imaging follow-up visit, the procedures required at both visits may be combined.

Follow-up visits to be scheduled to coincide with follow-up imaging. For participants continuing with imaging follow-up, if their 90-day Safety Follow-up visit falls within the same window as their imaging follow-up visit, these visits may be combined. All procedures required at the Safety Follow-up visit at 90 days will be performed at the imaging follow-up.

Participants who are eligible for retreatment with pembrolizumab (with or without lenvatinib) may have up to 4 safety follow-up visits, 2 after the Initial Treatment Period and 2 after the Second Course Treatment.

8.11.3.2 Imaging Follow-up Visits

Participants who discontinue study treatment for a reason other than disease progression will move into the Follow-up Phase and should be assessed by every 9 or 12 weeks according to the imaging schedule (or more frequently as needed) by clinic visit to monitor disease status. 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 poststudy 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.

All participants who discontinue study intervention prior to disease progression will continue to undergo tumor assessments every 9 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. After 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 (with or without lenvatinib) according to the criteria in Section 6.6.5 will move from the 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.

8.11.3.3 Survival Follow-up

Participants who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-up Phase and should be contacted by telephone approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

8.11.4 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) CCI [redacted]

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Phase 3 Randomized, Open-Label, Study of Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) Versus Chemotherapy for First-line Treatment of Advanced or Recurrent Endometrial Carcinoma (LEAP-001)

Treatment Assignment	Approximately 875 eligible participants (612 pMMR participants and approximately 263 dMMR participants) will be randomized to one of the following 2 treatment arms in a 1:1 ratio: • Arm 1: pembrolizumab plus lenvatinib • Arm 2: paclitaxel (or docetaxel for participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel, see Section 4.3.3.1) and carboplatin Randomization stratification factors include: • MMR status (pMMR versus dMMR), and if pMMR: - ECOG (0 versus 1) - Measurable disease (yes versus no) - Prior chemotherapy and/or chemoradiation (yes versus no) Eligible participants will first be stratified by MMR status (pMMR versus dMMR), then only within the pMMR stratum, participants will be further stratified according to ECOG (0 versus 1), measurable disease (yes versus no) and prior chemotherapy and/or chemoradiation (yes versus no). A total of 9 strata will be used for the study.
Analysis Populations	• Efficacy: Intent to Treat (ITT) • Safety: All Participants as Treated (APaT)
Primary Endpoints	• PFS based on RECIST 1.1 as assessed by BICR, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ • OS
Secondary Endpoints	• OR by BICR using RECIST 1.1 • Patient reported quality of life assessed by mean change from baseline of EORTC QLQ-C30 • Safety and tolerability of the 2 treatment arms
Statistical Methods for Key Efficacy Analyses	The primary hypotheses will be evaluated by comparing PFS and OS using a stratified log-rank test. The hazard ratio 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% CIs provided for between-group comparison; 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 [Miettinen, O. and Nurminen, M. 1985].
Interim Analyses	CCI [redacted]
Multiplicity	CCI [redacted] The graphical approach of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] will be applied to re-allocate alpha among the hypotheses of PFS and OS. CCI [redacted]

Sample Size and Power	The planned sample size is approximately 875 participants (612 pMMR participants and approximately 263 dMMR participants). CCI [redacted]

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 the Sponsor.

The Sponsor will generate the randomized allocation schedule for study intervention assignment for this protocol and the randomization will be implemented in IVRS/IWRS.

Although the study is open label, analyses or summaries generated by randomized treatment assignment, or actual treatment received status will be limited and documented. Further documentation will be provided in the sSAP. In addition, the independent radiologist(s) will perform the central imaging review without knowledge of treatment group assignment.

Blinding issues related to the planned interim analyses are described in Section 9.7.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

9.4 Analysis Endpoints

Efficacy, safety and PRO endpoints that will be evaluated for within- and/or between-treatment differences are listed below. Other endpoints will be described in the sSAP.

Primary

PFS is defined as the time from randomization to the first documented disease progression per RECIST 1.1 as assessed by BICR, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ or death due to any cause, whichever occurs first.

OS is defined as the time from randomization to death due to any cause.

Secondary

OR is defined as a confirmed CR or PR per RECIST 1.1 as assessed by BICR.

PRO endpoints will be assessed by mean change from baseline of the global score of the EORTC QLQ-C30.

Safety will be assessed by the number of AEs, SAEs, and irAEs and the number of participants discontinuing study intervention due to AEs

CCI

[redacted]

9.5 Analysis Populations

Extension Portion of the Study in China

After the sample size required for the Global Cohort is reached, the study will continue to randomize participants in China until the sample size for the Chinese participants meets the

target for China. The Chinese subjects randomized after the enrollment of the Global Cohort is closed will not be included in the primary analysis population which is based on the Global Cohort. The China Cohort may also be analyzed separately per local regulatory requirement.

9.5.1 Efficacy Analysis Populations

The 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 arm to which they are randomized.

9.5.2 Safety Analysis Populations

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all randomized/allocated participants who received at least 1 dose of study intervention. Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who take incorrect study intervention for the entire treatment period; such participants will be included in the treatment group corresponding to the study intervention actually received.

At least 1 laboratory, vital sign, or ECG measurement obtained after at least 1 dose of study intervention is required for inclusion in the analysis of the respective safety parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling safety analyses are provided in Section 9.6.2.

9.5.3 PRO Analysis Population

The PRO analyses are based on the PRO FAS population, defined as participants who have at least 1 PRO assessment available and have received at least 1 dose of study intervention.

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. CCI [redacted]

Statistical testing and inference for safety analyses are described in Section 9.6.2. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 9.8. Nominal p-values will be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity.

The stratification factors used for randomization (see Section 6.3.2) will be applied to all stratified analyses, in particular, the stratified log-rank test, stratified Cox model, and stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. If there

are small strata, for the purpose of analysis, strata will be combined to ensure sufficient number of participants, responses and events in each stratum. Details regarding the pooling strategy will be prespecified in the sSAP prior to the database lock for the first analysis when each applicable endpoint will be analyzed, and decisions regarding the pooling will be based on a blinded review of response and event counts by stratum.

9.6.1.1 Progression-free Survival (PFS)

The nonparametric 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. 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 6.3.2) 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. 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). Death is always considered as a PD event. Participants who do not experience a PFS event will be censored at the last disease assessment. Sensitivity analyses will be performed for comparison of PFS based on investigator's assessment.

To evaluate the robustness of the PFS endpoint per RECIST 1.1 based on BICR, one primary and 2 sensitivity analyses with a different set of censoring rules will be performed. For the primary analysis, if the events (PD or death) are immediately after more than one missed disease assessment, the data are censored at the last disease assessment prior to missing visits. Also data after new anticancer therapy are censored at the last disease assessment prior to the initiation of new anticancer therapy. The first sensitivity analysis follows the complete follow-up intention-to-treat principle. PDs/deaths are counted as events regardless of missed study visits or initiation of new anticancer therapy. The second sensitivity analysis, it considers discontinuation of treatment or initiation of an anticancer treatment after discontinuation of study-specified treatments, whichever occurs later, to be a PD event for participants without documented PD or death. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for primary and sensitivity analyses are summarized in Table 10.

Table 10 Censoring Rules for Primary and Sensitivity Analyses of Progression-free Survival

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 intervention.
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

An analysis of PFS2, defined as the time from randomization to subsequent disease progression after initiation of new anticancer therapy, or death from any cause, whichever first, will be performed. Participants alive and for whom a disease progression after initiation of new anticancer treatment has not been observed will be censored at the last time the participant was known to be alive and without disease progression. The same stratified Cox proportional hazard model will be used to estimate the HR and its 95% CI.

9.6.1.2 Overall Survival (OS)

The nonparametric 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 6.3.2). 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 6.3.2) 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. The Restricted Mean Survival Time (RMST) method may be conducted for OS to account for the possible nonproportional hazards effect.

9.6.1.3 Objective Response Rate (ORR)

Stratified Miettinen and Nurminen's method will be used for comparison of the objective response rate (ORR) between 2 treatment groups [Miettinen, O. and Nurminen, M. 1985]. The difference in ORR and its 95% confidence interval (CI) 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 6.3.2) will be applied to the analysis.

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 11.

Table 11 Efficacy Analysis Methods for Key Efficacy Endpoints

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses:			
PFS (RECIST 1.1) by BICR	Testing: Stratified Log-rank Test Estimation: Stratified Cox model with Efron's tie handling method.	ITT	Censored according to rules in Table 10.
OS	Testing: Stratified Log-rank Test Estimation: Stratified Cox model with Efron's tie handling method.	ITT	Censored at last known alive date.
Secondary Analyses:			
ORR (RECIST 1.1) by BICR	Testing: Stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985a].	ITT with measurable disease at baseline	Participants with missing data are considered nonresponders.
Sensitivity analyses will be performed for PFS, and ORR based on investigator's assessment.			

9.6.2 Statistical Methods for Safety Analyses

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 12). 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 or adverse events of special interest (AEOSIs) that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance. 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 plus lenvatinib included in this study has not been found to impact safety. 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 (via the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]).

Membership in Tier 2 requires that at least 10% of participants in any treatment group show 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 for Tier 2 events may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not 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 to 5 AE, a drug-related Grade 3 to 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.

Continuous Safety Measures

For continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Table 12 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	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
	Any AE leading to death		X
	Specific AEs, SOCs (incidence <10% 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 Methods for PRO Analyses

This section describes the planned analyses for the PRO endpoints.

To evaluate the treatment effect on the health-related QoL outcomes at prespecified time points, a constrained longitudinal data analysis (cLDA) model will be applied, with the PRO score as the response variable, and the treatment by time interaction and stratification factors as covariates. Least square mean (LS mean) change from baseline will be summarized. Group-wise comparisons will be performed, and model-based LS mean score will be provided by treatment group and study visit.

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 randomized, and the primary reason for discontinuation will be displayed. Demographic variables (such as age) and baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables. The reasons for exclusion from the ITT population (if any) will be summarized.

9.7 Interim Analyses

An eDMC will serve as the primary reviewer of the results of the interim analyses of the study and will make recommendations for discontinuation of the study or protocol modifications to an Executive Oversight Committee of the Sponsor. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this Executive Oversight Committee (and potentially other limited Sponsor personnel) may be unblinded to results at the treatment level to act on these recommendations. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the unblinded statistician. Additional logistical details will be provided in the eDMC Charter. Key aspects of the interim analyses are described in Section 9.7.2.

Treatment-level results from the interim analysis will be provided to the eDMC by the unblinded statistician. Prior to final study unblinding, the unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

9.7.1 Safety Interim Analyses

The eDMC will conduct regular safety interim analyses. The timing of these safety interim analyses will be specified in the eDMC charter.

9.7.2 Efficacy Interim Analyses

CCI

[redacted]

CCI

[redacted]

9.8 Multiplicity

The study uses the graphical method of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] to control multiplicity for multiple hypotheses as well as interim analyses. CCI

[redacted]

CCI

[redacted]

9.8.1 Efficacy Analyses

9.8.1.1 Progression-free Survival

CCI

[redacted]

CCI

9.8.1.2 Overall Survival

CCI

CCI

[redacted]

9.8.1.3 Safety Analyses

The eDMC has responsibility for assessment of overall risk: benefit. When prompted by safety concerns, the eDMC can request corresponding efficacy data. eDMC review of efficacy data to assess the overall risk: benefit to study participants will not require a multiplicity adjustment typically associated with a planned efficacy IA. However, to account for any multiplicity concerns raised by the eDMC review of unplanned efficacy data when

prompted by safety concerns, a sensitivity analysis for OS adopting a conservative multiplicity adjustment will be prespecified in the sSAP.

9.9 Sample Size and Power Calculations

The sample size is estimated based on the primary endpoints PFS and OS. Approximately 875 participants (including approximately 612 pMMR participants and approximately 263 dMMR participants) will be randomized in a 1:1 ratio for the global study.

The study will be considered to be fully enrolled when 612 pMMR participants have enrolled.

Sample size and power calculations are based on pMMR participants:

CCI

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the between-group treatment effect for PFS and OS (with a nominal 95% CI) will be estimated and plotted by treatment group within each category of the following classification variables:

- Stratification factors
  MMR status (pMMR versus dMMR)
  - If pMMR
    - ECOG (0 versus 1)
    - Measurable disease (yes versus no)
    - Prior chemotherapy and/or chemoradiation (yes versus no)

- Age group (<65 years versus ≥65 years)
- Race (white, non-white)

The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above. If the number of participants in a category of a subgroup variable is less than 10% of the ITT population, the subgroup analysis will not be performed for this category of the subgroup variable, and this subgroup variable will not be displayed in the forest plot.

9.11 Compliance (Medication Adherence)

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

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.

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

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (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 (eg, 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 (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that 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 (ie, 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-noncompliance 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 primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified 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 (eg, 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.

10.1.2 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 the Sponsor'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 the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor 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 the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that 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 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 the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor 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.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents 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 the Sponsor.

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.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor 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.

10.1.4 Committees Structure

10.1.4.1 Scientific Advisory Committee

The Scientific Advisory Committee 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.

10.1.4.2 Executive Oversight Committee

The EOC is comprised of members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the DMC regarding the study.

10.1.4.3 External 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. 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 (Section 9.7 Interim Analysis) 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 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.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor 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, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor 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.

10.1.6 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, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD 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 study 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.

10.1.7 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 GCP: 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 by MSD, is provided in this appendix under the Code of Conduct for Clinical Studies.

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 the Sponsor.

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

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor 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 Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor 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.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor 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 the Sponsor 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 the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor 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 the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). 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/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 16 will be performed by the local lab.
- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure and correspond with the time frame for female participant contraception in Section 5.1.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.
- 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.
- 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.
- Additional laboratory assessments required per standard of care for the chemotherapy arm, but not included here, should be obtained per local guidance.

Table 16 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils		
	RBC Count			
	Hemoglobin			
	Hematocrit			
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 (TSH)[c]	Free thyroxine (FT4)[c]
	Albumin	Cholesterol	Glucose	Triiodothyronine (T3)[c]
	Total protein		Amylase	Lipase[d]
		Lactate dehydrogenase		
Urinalysis/Urine dipstick testing[e]	Specific gravity Glucose, hemoglobin or blood, ketones, pH, protein[f], by dipstick			
Other Tests	PT/INR and aPTT/PTT[g] Serum or urine β human chorionic gonadotropin (β hCG) pregnancy test (as needed for WOCBP)[h] Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)] if required by local health authority			

Abbreviations: aPTT = activated partial thromboplastin time; 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 C1, retrospective review of thyroid function testing results is allowed when the results are not available prior to dosing.
d. After Cycle 1 Day 1, retrospective review of lipase and amylase results is allowed when the results are not available prior to dosing.
e. 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.
f. 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 performed to quantify the 24-hour urine protein excretion.
g. Performed as part of the screening assessment and as clinically indicated for participants taking anticoagulation therapy.
h. WOCBP require negative test prior to randomization and within 24 hours prior to first dose. If less than 24 hours have elapsed between the randomization test and the first dose of study intervention, another pregnancy test is not required prior to starting study intervention.

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product for a perceived psychological or physiological reward or desired non-therapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- 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 intervention.
- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor 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, 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 intervention 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 intervention 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 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). Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 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 8.4.6 for protocol-specific exceptions.

10.3.3 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 an MSD product and is documented in the participant'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) that 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 1 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.

10.3.4 Additional Events Reported in the Same Manner as SAE

Additional events that 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 the Sponsor in the same time frame as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose

10.3.5 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 the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. 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 the Sponsor.
- 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/toxicity

- 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 for Adverse Events (CTCAE), version v. 4.0. Any AE that 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 Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product 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 the Sponsor's product 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 the Sponsor's product 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 the Sponsor's product? 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 the Sponsor's product 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 the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

  - **Rechallenge:** Was the participant re-exposed to the Sponsor's product 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) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE

MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INIRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the case report forms/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 Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship:
  - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
  - No, there is not a reasonable possibility of Sponsor's product relationship:
  - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (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 the Sponsor. 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 the Sponsor.
- 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 1 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 by Sponsor 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 the Sponsor within 24 hours of receipt of the information.

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

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

- The primary mechanism for reporting to the Sponsor 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 Study File Binder (or equivalent).

SAE reporting to the Sponsor 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 the Sponsor.
- 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 Study File Binder (or equivalent).

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

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

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Műllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

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 FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 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.

10.5.2 Contraception Requirements

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to consistent and correct use of a highly effective method of contraception as described in Table 17 during the protocol-defined time frame in Section 5.1.

Table 17 Highly Effective Contraception Methods

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly*
• Progestogen-only subdermal contraceptive implant[b,c] • IUS[c,] • IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This 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. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
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 intervention. 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.
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. b. If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. c. IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: • Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. • Male condom with cap, diaphragm, or sponge with spermicide. • Male and female condom should not be used together (due to risk of failure with friction).

10.5.3 Pregnancy Testing

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 24 hours or the first dose of study intervention.

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test and in accordance with local requirements.

After initiation of treatment, additional pregnancy testing will be performed at monthly intervals during the treatment period and at least every 30 days up to 120 days post last dose of pembrolizumab or 30 days post the last dose of lenvatinib, whichever comes last, (up to 180 days for participants receiving chemotherapy), and as required locally.

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

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

Not Applicable.

10.7 Appendix 7: Country-specific Requirements

10.7.1 Canada

Please refer to the current lenvatinib product monograph for management of AEs associated with lenvatinib administration.

Section 6.6.1.9 Management of Gastrointestinal Perforation or Fistula Formation

Lenvatinib should be discontinued in any participant who develops gastrointestinal perforation of any grade or ≥ Grade 3 fistula.

10.7.2 Germany

Laboratory Testing

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

10.8 Appendix 8: Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological PD by RECIST 1.1 as determined by the investigator, the investigator will decide whether to continue a participant on study intervention until repeat imaging is obtained (using iRECIST for participant management) (see Table 8 and Figure 2). This decision by the investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed clinically unstable should be discontinued from study intervention at central verification of site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the investigator decides to continue treatment, the participant may continue to receive study intervention and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment. Images should continue to be sent in to the central imaging vendor for potential retrospective BICR.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir

Note: The iRECIST publication uses the terminology "sum of measurements,", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.

Unequivocal progression of nontarget lesion(s) identified at baseline

Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and nontarget lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or nonmeasurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Nontarget.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

Any of the factors that were the basis for the iUPD at the previous visit show worsening

For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared with any prior iUPD time point

For nontarget lesions, worsening is any significant growth in lesions overall, compared with a prior iUPD time point; this does not have to meet the “unequivocal” standard of RECIST 1.1

For new lesions, worsening is any of these:

An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point

Visible growth of new nontarget lesions

The appearance of additional new lesions

Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

None of the progression-confirming factors identified above occurs AND

The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

None of the progression-confirming factors identified above occurs, AND

The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudoprogression, and the level of suspicion for progression is “reset.” This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management After the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit or if RECIST 1.1 PD has not been verified centrally, an exception to continue study intervention may be considered after consultation with the Sponsor. In this case, if study intervention is continued, tumor imaging should continue to be performed after the intervals as outlined in Section 1.3 and submitted to the central imaging vendor.

Detection of Progression at Visits After Pseudoprogression Resolves

After resolution of pseudoprogression (ie, achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

Target lesions

Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudoprogression. The nadir is always the smallest sum of diameters seen during the entire study, either before or after an instance of pseudoprogression.

Nontarget lesions

If nontarget lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.

If nontarget lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of nontarget lesions, taken as a whole.

New lesions

New lesions appear for the first time

Additional new lesions appear

Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum

Previously identified nontarget lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: If new lesions occurred at a prior instance of iUPD, and at the Confirmatory Imaging, the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication [Seymour, L., et al 2017].

10.9 Appendix 9: 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].

10.10 Appendix 10: 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 1994a].

10.11 Appendix 11: Clinical Studies Evaluating Drug-Drug Interactions With Lenvatinib

Nonclinical studies identify CYP3A4 as a potentially important Cytochrome P450 isozyme responsible for metabolism of lenvatinib. Clinical studies were conducted to test these findings.

Simultaneous CYP3A4/P-glycoprotein (Pgp) inhibition by ketoconazole slightly (15% to 19%) increases systemic exposure to lenvatinib [Shumaker, R., et al 2015]. Since no change was observed in half-life, t_{max}, or lag time (t_{lag}), the slight increase in systemic exposure is probably related to a decrease in first pass metabolism. However, since the magnitude of change is small, co-administration of lenvatinib with CYP3A4/Pgp inhibitors is not of clinical concern.

The influence of Pgp inhibition on lenvatinib PK has been investigated. Pgp inhibition was accomplished by co-administering a single dose of rifampin with a single dose of lenvatinib. Preliminary results suggest Pgp inhibition increases systemic exposure to lenvatinib 26% to 32%. Thus, co-administration of lenvatinib with Pgp inhibitors only causes a small increase in lenvatinib exposure.

The influence of simultaneous Pgp and CYP3A4 induction on lenvatinib PK has been investigated. Examination of simultaneous Pgp and CYP3A4 induction on lenvatinib PK was accomplished by administering rifampin QD for 21 days [Shumaker, R. C., et al 2014]. A single dose of lenvatinib was co-administered with the 15th dose of rifampin. Based on preliminary data, simultaneous Pgp and CYP3A4 induction minimally altered lenvatinib exposure as mean C_{max} increased about 8% while AUC decreased about 7%. Co-administration of lenvatinib with CYP3A4/Pgp inducers is not of clinical concern.

The main metabolic pathways for lenvatinib in humans were identified as enzymatic (CYP3A and aldehyde oxidase) and nonenzymatic processes (Lenvima Product Information).

10.12 Appendix 12: Justification of Non-inferiority Margin

The Sponsor conducted a systematic literature review (SLR) to gather clinical trial evidence on the efficacy and safety of carboplatin and paclitaxel combination therapy for the first line (1L) treatment of patients with advanced (unresectable and/or metastatic) or recurrent endometrial carcinoma to justify a NI margin for hypothesis H3 (the combination of pembrolizumab plus lenvatinib is non-inferior to chemotherapy with respect to OS in pMMR participants) in LEAP-001/ENGOT-EN9. The SLR focused on studies evaluating the efficacy and safety of treatments for patients with advanced or metastatic endometrial carcinoma.

A total of 3,217 abstracts were identified from a literature search of MEDLINE, EMBASE, and Cochrane databases, and no additional records were identified through other sources such as the ASCO, ESMO, ISPOR conference proceedings and the US clinical trial registries. After excluding 599 duplicate citations, a total of 2,618 abstracts were screened to 257 full texts for the following reasons: duplicate publication (n = 47), study design (n = 571), population (n = 1,119), intervention (n = 27), other (n = 597). Of the 257 full text articles screened, 45 were excluded: 3 due to study design; 24 due to population not of interest; 2 due to interventions not of interest; 1 due to other reasons (such as reviews, editorials, comments, etc.); 3 due to duplicate publication; and 12 that did not provide outcomes for the population of interest to this review. A final number of 212 citations, testing interventions for treatment naïve and previously treated advanced endometrial patient populations, were retained. These publications were screened independently by 2 reviewers and decisions were reconciled. Of these, 7 primary publications (5 were single-arm studies and 2 were randomized controlled trials) were included in the evidence synthesis (see Table 8: Trial characteristics, study identifier in the SLR), reflecting the state of the evidence on the treatment of patients with previously untreated advanced (unresectable and/or metastatic) or recurrent endometrial carcinoma.

Of the 7 primary publications included in the evidence synthesis, carboplatin + paclitaxel was used in the randomized controlled setting in only 2 studies, Miller 2012 (vs doxorubicin + cisplatin + paclitaxel), and Matei 2017 (vs cisplatin + irradiation + carboplatin + paclitaxel) [Matei, D., et al 2017]. The median OS was only reported in Miller (2012) (32 months for paclitaxel + carboplatin and 38 months for doxorubicin + cisplatin + paclitaxel, HR = 1.01, 90% upper confidence limit = 1.16) [Miller, D., et al 2015]. Therefore, it is not feasible to derive a NI margin based on a meta-analysis of existing studies.

Nevertheless, with use of a NI margin of 1.1 in LEAP-001/ENGOT-EN-9, the HR boundary for H3 is 0.83 based on retaining 50% of the assumed effect of chemotherapy versus placebo. This margin is lower than the 90% upper confidence limit from the Miller 2012 publication. The margin of 1.1 is also the lower bound of the range of margins for non-inferiority cancer trials that used time-to-event primary outcomes [Riechelmann, R. P., et al 2013].

Therefore, based on this information, the Sponsor believes the prespecified NI margin of 1.1 in LEAP-001/ENGOT-EN9 represents a meaningful measure for testing the non-inferiority hypotheses in this study.

10.13 Appendix 13: Abbreviations

Abbreviation	Expanded Term
ADA	antidrug antibodies
ADL	activities of daily living
AE	adverse event
AEOSI	adverse events of special interest
ALT	alanine transaminase
APaT	All Participants as Treated
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
AUC	area under the concentration-time curve
AxIMP	auxiliary medicinal product
BCG	*Bacillus* Calmette–Guérin
BICR	blinded independent central review
BOR	best overall response
BP	blood pressure
CB	clinical benefit
CBR	clinical benefit rate
CD	cluster of differentiation
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval(s)
cLDA	constrained longitudinal data analysis
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CPMP	Committee for Proprietary Medicinal Products
CR	complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CYP	Cytochrome P450
CYP3A4	Cytochrome P450 3A4
DC	disease control
DCR	disease control rate
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
dMMR	mismatch repair deficient
DNA	deoxyribonucleic acid
DOR	duration of response
DVT	deep vein thrombosis
EC	endometrial carcinoma (or cancer)
ECG	electrocardiogram
ECHO	echocardiogram
ECI	event(s) of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data collection
eDMC	external Data Monitoring Committee
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC	European Organization for Research and Treatment of Cancer
EORTC-QLG	EORTC Quality of Life Group

Abbreviation	Expanded Term
EORTC-QLQ-C30	EORTC Quality of Life Questionnaire Core 30
EORTC-QLQ-EN24	EORTC Quality of Life Questionnaire Endometrial Cancer Module
EOT	End of treatment
ePRO	electronic patient-report outcomes
EuroQoL EQ-5D-5L	European Quality of Life eEuroQol-5 Dimensions 5-Level
FA	final analysis
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FFPE	formalin-fixed, paraffin-embedded
FGF	fibroblast growth factor
FIGO	International Federation of Gynecology and Obstetrics
FSH	follicle stimulating hormone
FT3	free T3
FT4	free T4
GCP	Good Clinical Practice
H	hypothesis
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	Hurthle cell cancer
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	hazard ratio
HRQoL	health-related quality of life
HRT	hormone replacement therapy
HUVEC	human umbilical vein endothelial cell
IA	interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
iCPD	immune-related confirmed radiographic disease progression
iCR	immune-related complete response
iCRO	imaging contract research organization
ID	identification
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG4	immunoglobulin G4
IgV	Ig-variable
IHC	immunohistochemistry
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
iPD	immune-related progressive disease
iPR	immune-related partial response
irAEs	immune-related adverse events
IRB	Institutional Review Board
iRECIST	modified RECIST 1.1 for immune-based therapeutics
IRR	independent radiologic review
IRT	interactive response technology
iSD	immune-related stable disease
ITT	Intention-to-Treat
IUD	intrauterine device
iUPD	Immune-related unconfirmed progressive disease
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic
IVRS	Interactive Voice Response System

Abbreviation	Expanded Term
IWRS	Integrated Web Response System
LS mean	least square mean
LVEF	left ventricular ejection fraction
MMR	mismatch repair
mRECIST	modified RECIST
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MSI-H	MSI-high
MSS	microsatellite stable
MTD	maximum tolerated dose
MUGA	multigated acquisition
nAb	neutralizing antibodies
NCI	National Cancer Institute
NDA	New Drug Application
NIMP	Non Investigational Medicinal Product
NSCLC	non-small cell lung cancer
ONJ	Osteonecrosis of the jaw
OR	objective response
ORR	objective response rate
OS	overall survival
PBPK	physiologically-based PK
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
PDLC	predefined limits of change
PFS	progression-free survival
PFS2	progression-free survival on next line therapy
Pgp	P-glycoprotein
PK	pharmacokinetic(s)
PKCθ	protein kinase C-theta
pMMR	mismatch repair proficient
PR	partial response
PRES	Posterior Reversible Encephalopathy Syndrome
PRO	Patient-reported Outcomes
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q3W	every 3 weeks
Q9W	every 9 weeks
Q12W	every 12 weeks
QD	once daily
QoL	quality-of-life
QP2	Department of Quantitative Pharmacology and Pharmacometrics
QTc	QT interval corrected
QTcF	QTc Fridericia formula
RCC	renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RMST	Restricted Mean Survival Time
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RPLS	Reversible Encephalopathy Syndrome/Reversible Posterior Leukoencephalopathy Syndrome
RR	respiratory rate
RTK	receptor tyrosine kinase
RUQ	right upper quadrant
SAC	Scientific Advisory Committee

Abbreviation	Expanded Term
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIM	Site Imaging Manual
SNP	single nucleotide polymorphisms
SoA	Schedule of Activities
SOC	System Organ Class
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
T3	triiodothyronine
T4	thyroxine
TAM	tumor associated macrophage
TAP	doxorubicin, cisplatin, and paclitaxel
TB	tuberculosis
TBL	total bilirubin
TC	paclitaxel and carboplatin
TEAE	treatment emergent adverse events
TMDD	target-mediated drug disposition
T-regs	regulatory T-cells
TSH	thyroid stimulating hormone
ULN	upper limit of normal
UPCR	urine protein-to-creatinine ratio
US	United States
VEGF	vascular endothelial growth factor
W27	Week 27
W54	Week 54
WBRT	whole brain radiation therapy
WES	whole exome sequencing
WOCBP	woman/women of childbearing potential
ZAP70	zeta-chain-associated protein kinase

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