Official Protocol Title:	A Phase 3 Randomized, Placebo-controlled Study to Evaluate the Safety and Efficacy of Pemetrexed + Platinum Chemotherapy + Pembrolizumab (MK-3475) with or without Lenvatinib (E7080/MK-7902) as First-line Intervention in Participants with Metastatic Nonsquamous Non small Cell Lung Cancer (LEAP-006)
NCT number:	NCT03829319
Document Date:	27-October-2023

Title Page

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Protocol Title: A Phase 3 Randomized, Placebo-controlled Study to Evaluate the Safety and Efficacy of Pemetrexed + Platinum Chemotherapy + Pembrolizumab (MK-3475) with or without Lenvatinib (E7080/MK-7902) as First-line Intervention in Participants with Metastatic Nonsquamous Non-small Cell Lung Cancer (LEAP-006)

Protocol Number: MK-7902-006-08 (E7080-G000-315)

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 cofunded 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	140221
EudraCT	2018-003824-35

Approval Date: 27 October 2023

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
7902-006-08	27-OCT-2023	The study is to be discontinued based on the observation that the combination of pembrolizumab + platinum chemotherapy + lenvatinib versus pembrolizumab + platinum chemotherapy did not meet the prespecified criteria for the primary endpoint of OS at the final analysis and the second dual primary endpoint of PFS at IA3.
7902-006-07	06-OCT-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.
7902-006-06	03-SEP-2021	Country-specific clarifications were added to address the sourcing of pembrolizumab in the UK and to clarify pembrolizumab dose modification and toxicity management in Canada.
7902-006-05	30-APR-2021	The protocol was amended to update the assumptions and timing of the analyses in the SAP to allow sufficient duration of follow-up based on updated enrollment period and the long-term survival data from the reference study KEYNOTE-189.
7902-006-04 – China-Specific	03-MAR-2020	The protocol was amended to extend the enrollment period beyond the global study to achieve required exposure and number of events to investigate efficacy and safety in participants with 1L NSCLC enrolled in China.
7902-006-03	09-AUG-2019	The study protocol was amended to correct significant clerical errors inadvertently introduced into study amendment 02 that altered the study protocol inclusion/exclusion criteria and contraceptive language.
7902-006-02	02-JUL-2019	Amended text to address health authority feedback and to align with the Sponsor's newly released lenvatinib and pembrolizumab (LEAP) program protocol template.

Document	Date of Issue	Overall Rationale
7902-006-01	16-JAN-2019	The protocol was amended in response to the feedback from the regulatory agency (FDA) regarding a potential hold comment related to permanent discontinuation of lenvatinib for Grade 3 thromboembolic events since CTCAE V5 classifies Grade 3 as "Urgent medical intervention indicated".
7902-006-00	08-NOV-2018	Original protocol

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 08

Overall Rationale for the Amendment:

The study is to be discontinued based on the observation that the combination of pembrolizumab + platinum chemotherapy + lenvatinib versus pembrolizumab + platinum chemotherapy did not meet the prespecified criteria for the primary endpoint of OS at the final analysis and the second dual primary endpoint of PFS at IA3.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 1.1, Synopsis	Clarify that the study is to be discontinued based on a lack of additional clinical benefit on overall survival of the combination of pembrolizumab plus lenvatinib over pembrolizumab monotherapy. Upon study termination, participants are discontinued and may be enrolled in a pembrolizumab extension study, if available.	This change addresses new data that recently became available. The combination of pembrolizumab + platinum chemotherapy + lenvatinib versus pembrolizumab + platinum chemotherapy did not meet the prespecified criteria for the primary endpoint of OS at the final analysis and the second dual primary endpoint of PFS at IA3..

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 1.1, Synopsis	The changes specify which analyses and procedures will or will not continue to be conducted.	Refer to Section 1.1 rationale.
Section 1.1, Synopsis	Table: Intervention Groups and Duration: To clarify that hat the study is to be discontinued based on a lack of additional clinical benefit on overall survival of the combination of pembrolizumab plus lenvatinib over pembrolizumab monotherapy. Upon study termination, participants are discontinued and may be enrolled in a pembrolizumab extension study, if available.	Refer to Section 1.1 rationale .
Section 1.3, Schedule of Activities	Clarify which activities will or will not be performed during the study for participants who are still on study treatment.	Refer to Section 1.1 rationale.
Section 4.3.1, Maximum Dose/Exposure for This Study	Note on study-specific investigator letter has been added.	Refer to Section 1.1 rationale.
Section 4.4, Beginning and End of Study Definition	Participants may be enrolled in an extension study.	Refer to Section 1.1 rationale.

Section Number and Name	Description of Change	Brief Rationale
Section 6.1, Study Intervention(s) Administered	Note on study-specific investigator letter has been added.	Refer to Section 1.1 rationale.
Section 6.3.3, Blinding	Study unblinded due to result of FA.	Refer to Section 1.1 rationale.
Section 6.6, Dose Modification (Escalation/Titration/Other)	Treatment of participants with study interventions is clarified. Note on study-specific investigator letter has been added.	Refer to Section 1.1 rationale.
Section 7.1.1, Second Course Treatment	Clarify that participants will be considered for Second Course treatment following investigator assessment of PD.	Refer to Section 1.1 rationale.
Section 8.1.10, Participant Blinding/Unblinding	Study unblinded due to results of final analysis	Refer to Section 1.1 rationale.
Section 8.2.1, Tumor Scans and Response Assessment	Central tumor response assessments will be discontinued. Imaging scans will no longer be submitted to the iCRO nor read by BICR.	Refer to Section 1.1 rationale.
Section 8.2.1.3, End of treatment and Follow-up Tumor Scans	Follow-up tumor imaging is only required for participants who are candidate for Second Course treatment.	Refer to Section 1.1 rationale.
Section 8.2.2, Patient-Reported Outcomes	ePRO assessments will be discontinued.	Refer to Section 1.1 rationale.
Section 8.4.1, Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information	Text for participants who enter the separate Extension Study was added.	Refer to Section 1.1 rationale.
Section 8.6, Pharmacokinetics	Sample collection will be discontinued.	Refer to Section 1.1 rationale.
Section 8.9, Biomarkers	Sample collection will be discontinued.	Refer to Section 1.1 rationale.
Section 8.12.2, Treatment Period	BICR verification was removed.	Refer to Section 1.1 rationale.
Throughout Document	Minor administrative, formatting, grammatical, and typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3 Randomized, Placebo-controlled Study to Evaluate the Safety and Efficacy of Pemetrexed + Platinum Chemotherapy + Pembrolizumab (MK-3475) with or without Lenvatinib (E7080/MK-7902) as First-line Intervention in Participants with Metastatic Nonsquamous Non-small Cell Lung Cancer (LEAP-006)

Short Title: A Phase 3 Study of Pemetrexed + Platinum Chemotherapy + Pembrolizumab with or without Lenvatinib in Participants with NSCLC

Acronym: Protocol 006

Hypotheses, Objectives, and Endpoints:

The objectives of the study are as follows, in participants with nonsquamous non-small cell lung cancer (NSCLC), who are at least 18 years of age.

NOTE: Based on the data from the final safety and efficacy analysis for LEAP-006 (data cutoff 11-AUG-2023), the combination of pembrolizumab + platinum chemotherapy + lenvatinib versus pembrolizumab + platinum chemotherapy did not meet the pre-specified criteria for the primary endpoint of OS at the final analysis and the second dual primary endpoint of PFS at IA3. Based upon these data, the study was unblinded as of 20-SEP-2023. Safety analysis will be performed at the end of the study; there will be no further analyses for efficacy and ePRO endpoints.

NOTE: In alignment with the study-specific investigator letter dated 20-SEP-2023, all study participants still receiving study treatment should continue to receive therapy on study and undergo modified protocol study procedures as specified in this amendment. Participants currently on study treatment with lenvatinib can continue treatment per investigator's discretion. Participants who are potential candidates for Second Course treatment will continue in Efficacy Follow up.

As of Amendment 08, participants who are still on study treatment will no longer require tumor response assessments by BICR to be performed. Scans will no longer be submitted to the iCRO. Participants who are still on study medication should continue tumor imaging assessment as assessed by investigator per protocol. Biomarker and PK specimen collection is discontinued.

Primary Objectives	Primary Endpoints
- Part 1: To evaluate the safety and tolerability of treatment with lenvatinib + platinum doublet chemotherapy + pembrolizumab.	- Dose-limiting toxicities (DLTs), adverse events (AEs) and study intervention discontinuations due to AEs.
- Part 2: To compare progression free survival (PFS) as assessed by blinded independent central review (BICR) according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) for lenvatinib + platinum doublet chemotherapy + pembrolizumab versus matching placebo + platinum doublet chemotherapy + pembrolizumab. - Hypothesis (H1): The combination of lenvatinib +platinum doublet chemotherapy + pembrolizumab prolongs PFS per RECIST 1.1 by BICR compared to matching placebo + platinum doublet chemotherapy + pembrolizumab.	- PFS, defined as the time from randomization to the date of the first documentation of disease progression or death from any cause, whichever is earlier.
- Part 2: To compare overall survival (OS) for the combinations of lenvatinib + platinum doublet chemotherapy + pembrolizumab versus matching placebo + platinum doublet chemotherapy + pembrolizumab. - Hypothesis (H2): The combination of lenvatinib + platinum doublet chemotherapy + pembrolizumab prolongs OS compared to matching placebo + platinum doublet chemotherapy + pembrolizumab.	- OS, defined as the time from randomization to the date of death from any cause.

Secondary Objectives	Secondary Endpoints
- Part 2: To compare objective response rate (ORR) as assessed by BICR according to RECIST 1.1 for the combinations of lenvatinib + platinum doublet chemotherapy + pembrolizumab versus matching placebo + platinum doublet chemotherapy + pembrolizumab. - Hypothesis (H3): The combination of lenvatinib + platinum doublet chemotherapy + pembrolizumab has superior ORR per RECIST 1.1 by BICR compared to matching placebo + platinum doublet chemotherapy + pembrolizumab.	- Objective response (OR), defined as a confirmed complete response (CR) or partial response (PR).
- Part 2: To evaluate duration of response (DOR) per RECIST 1.1 by BICR for the combinations of lenvatinib + platinum doublet chemotherapy + pembrolizumab and matching placebo + platinum doublet chemotherapy + pembrolizumab.	- DOR, defined as the time from the first documented evidence of CR or PR until disease progression or death due to any cause (whichever is earlier), for participants who demonstrate a confirmed CR or PR.
- Part 2: To evaluate the safety and tolerability for the combinations of lenvatinib + platinum doublet chemotherapy + pembrolizumab and matching placebo + platinum doublet chemotherapy + pembrolizumab.	- Adverse events (AEs) and study intervention discontinuations due to AEs.
- Part 2: To evaluate the mean change from baseline in global health status/quality of life (QoL), cough, chest pain, dyspnea, and physical functioning for the combinations of lenvatinib + platinum doublet chemotherapy + pembrolizumab and matching placebo + platinum doublet chemotherapy + pembrolizumab.	- Change from baseline for the following patient-reported outcomes (PRO) scales/items: global health status/QoL (EORTC QLQ-C30 Items 29 and 30), cough (EORTC QLQ-LC13 Item 31), chest pain (EORTC QLQ-LC13 Item 40), dyspnea (EORTC QLQ-C30 Item 8), and physical functioning (EORTC QLQ-C30 Items 1 through 5).

- Part 2: To evaluate the time to true deterioration (TTD) in global health status/QoL, cough, chest pain, dyspnea, and physical functioning for the combinations of lenvatinib + platinum doublet chemotherapy + pembrolizumab and matching placebo + platinum doublet chemotherapy + pembrolizumab.	- TTD, defined as the time from baseline to the first onset of a ≥10-point deterioration from baseline with confirmation by the subsequent visit of a ≥10-point deterioration from baseline in global health status/QoL (EORTC QLQ-C30 Items 29 and 30), cough (EORTC QLQ-LC13 Item 31), chest pain (EORTC QLQ-LC13 Item 40), dyspnea (EORTC QLQ-C30 Item 8), and physical functioning (EORTC QLQ-C30 Items 1 through 5). - TTD in the composite endpoint (combination of cough [QLQ-LC13 item 31], chest pain [QLQ-LC13 item 40], or dyspnea [QLQ-C30 item 8]) defined as the time to first onset of a ≥10-point deterioration from baseline in any one of 3 scale items with confirmation by the subsequent visit of a ≥10-point deterioration from baseline in the same scale as the first onset

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	First-line treatment of metastatic NSCLC
Population	Adult participants with treatment-naïve, metastatic nonsquamous NSCLC
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.

Type of Control	Placebo control
Study Blinding	Double-blind
Masking	Investigator Participant Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact. Extension Study in China: The Sponsor estimates that the study will require approximately 1 additional year (beyond the global study's last participant last study-related contact) from the time the first participant (or their legally acceptable representative) provides informed consent until the last participant's last study-related contact.

Number of Participants:

Global Study: The planned sample size for Part 1 (safety run-in) is approximately 12 participants. The planned sample size for Part 2 (Phase 3 study) is approximately 714 participants with approximately 357 participants in each treatment arm.

Extension Study in China: Approximately 200 participants overall will be enrolled in China, including participants enrolled in either the global study or the extension study.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Part 1 and Part 2: Arms 1 and 2	Carboplatin or Cisplatin	AUC 5 mg/mL/min (carboplatin) 75 mg/m^2 (cisplatin)	Q3W	IV	4 cycles	Standard of care
	Pemetrexed	500 mg/m^2	Q3W	IV	4 cycles with possibility of maintenance therapy until reaching a discontinuation criterion[1]	Standard of care
	Pembrolizumab	200 mg	Q3W	IV	Up to 35 cycles	Standard of care/Experimental
Part 1 and Part 2: Arm 1	Lenvatinib	8 mg	Once daily	Oral	Until reaching a discontinuation criterion[1]	Experimental
Part 2: Arm 2	Matching placebo	N/A	Once daily	Oral	Until reaching a discontinuation criterion[1]	Placebo

Abbreviations: AUC = area under the plasma drug concentration-time curve; BICR = blinded independent central review; iRECIST = Response Evaluation Criteria in Solid Tumors version 1.1 for immune-based therapeutics; IV = intravenous(ly); N/A = not applicable; Q3W = once every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors

1. Radiographically documented disease progression verified by BICR per RECIST 1.1, and only when clinically appropriate, confirmed by the site per iRECIST, unacceptable toxicity, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw treatment, participant withdrawal of consent, pregnancy, noncompliance with study intervention or procedure requirements, or administrative reasons requiring cessation of treatment.

Total Number	2 (Part 2)

Duration of Participation	Each participant will participate in the study from the time the participant provides documented informed consent through the final study-related contact. After a screening phase of 28 days, each participant will be assigned to receive study intervention until one of the conditions for discontinuation of study intervention is met. Participants treated with pembrolizumab who complete 35 cycles of treatment with stable disease (SD) or better or participants who attain an investigator-determined CR and have received at least 8 cycles of pembrolizumab may be eligible for retreatment with up to an additional 17 cycles (approximately 1 year) of pembrolizumab if they experience radiographic disease progression after stopping treatment in the initial treatment phase. This retreatment is termed Second Course Treatment. Participants may also continue treatment with lenvatinib/matching placebo during Second Course Treatment at the discretion of the investigator until meeting one of the criteria for treatment discontinuation. Participants will be permitted to continue study intervention beyond RECIST 1.1-defined disease progression as long as the treating investigator considers that the participant may experience clinical benefit with continued treatment per iRECIST, and the participant is tolerating study intervention. All decisions to continue treatment beyond 2 consecutive scans (at least 4 weeks apart) showing progression must be approved by the Sponsor. After study intervention completion/discontinuation, each participant will be followed for safety as described in Section 8.4. Participants who complete or discontinue study intervention in the absence of radiographic disease progression will have posttreatment follow-up imaging for disease status 6 weeks, 12 weeks, 18 weeks, 27 weeks, 36 weeks, 45 weeks, and 54 weeks from the day of randomization, as applicable, and every 12 weeks thereafter until disease progression is documented radiographically per RECIST 1.1 and verified by BICR, initiating a new anticancer therapy, participant withdrawal of consent, pregnancy, becoming lost to follow-up, death, or the end of the study, whichever is earlier. After confirmed disease progression or initiation of a new anticancer therapy, each participant will be contacted by telephone every 12 weeks to assess survival status until participant withdrawal of consent, becoming lost to follow-up, death, or the end of the study, whichever is earlier. The end of the study will be when the last participant completes the last study-related telephone call or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

	The study is to be discontinued based on the observation that the combination of pembrolizumab + platinum chemotherapy + lenvatinib versus pembrolizumab + platinum chemotherapy did not meet the prespecified criteria for the primary endpoint of OS at the final analysis and the second dual primary endpoint of PFS at IA3. Upon study termination, participants are discontinued and may be enrolled in a pembrolizumab extension study, if available.

Study Governance Committees:

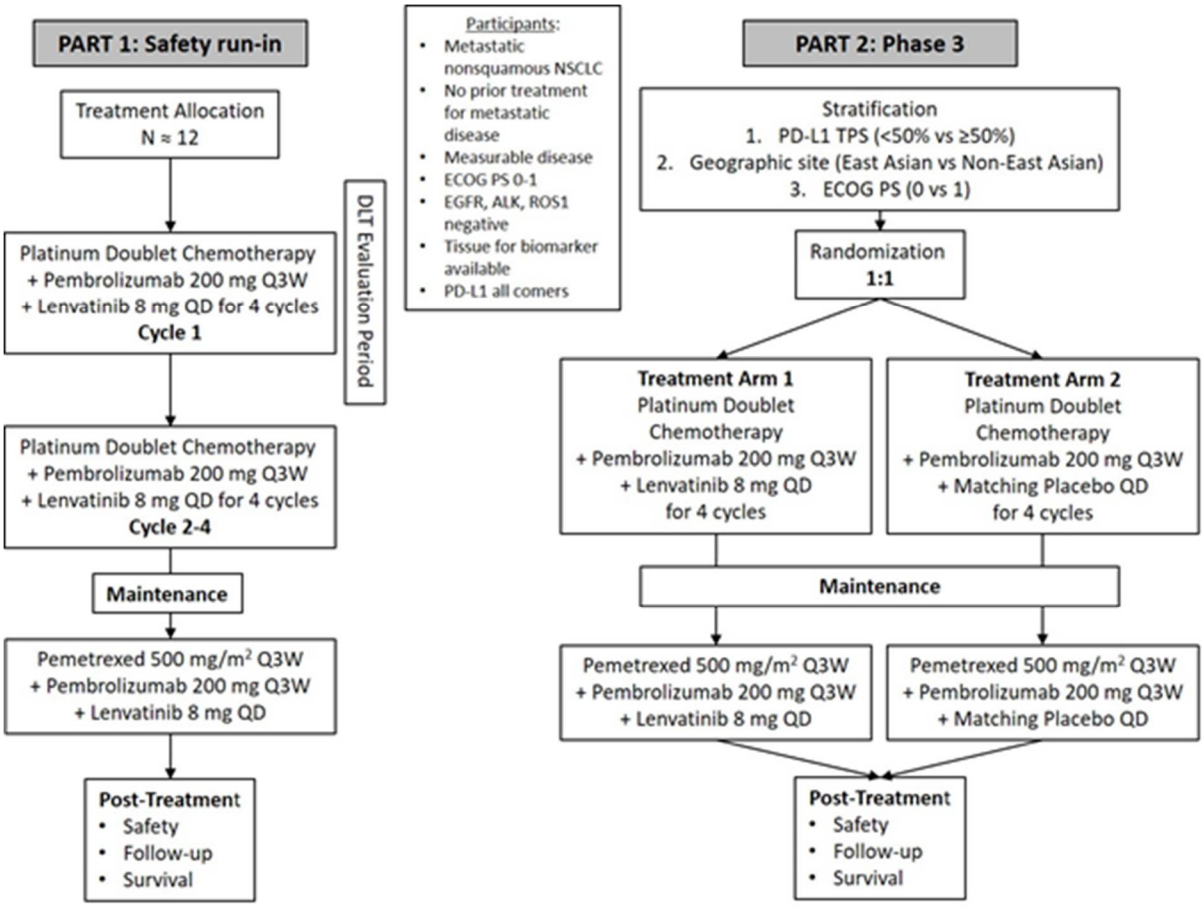
Steering Committee	Yes
Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1.	

Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 8.

1.2 Schema

The study design is depicted in Figure 1.



Abbreviations: ALK = anaplastic lymphoma kinase; DLT = dose-limiting toxicity; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; PD-L1 = programmed death ligand 1; PS = performance status; Q3W = once every 3 weeks; qd = once daily; ROS1 = c-ros oncogene 1; TPS = tumor proportion score

Figure 1 Study Schema

1.3 Schedule of Activities (SoA)

1.3.1 Initial Treatment Phase - Parts 1 and 2

Study Period	**Screen-ing**	**Treatment Cycle = 21 days**										**EOT**	**Post treatment**			**Notes**
													Safety[2]	**Follow-up[3]**	**Survival**	
Visit Timing[1]/Cycle Number	**-28 to -1**	**1**			**2**		**3**	**4**	**5**	**6-35**	**>36**		**30 Days post last dose**	**Every 6/9/12 Weeks**	**Every 12 Weeks**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 for visit details.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (Days)		**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At D/C**	**+ 7**	**± 7**	**± 14**	
Administrative Procedures																
Informed Consent Form	X															The ICF must be documented prior to any protocol-specific procedures are performed. Additional consent is required at disease progression.
Inclusion/Exclusion Criteria	X															
Participant ID Card	X	X														Update at C1D1.
Demographics and Medical History	X															
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X			Prior medications taken within 30 days before the first dose of study intervention and concomitant medications taken during the study and for 30 days after the last dose of study intervention (or 90 days if used to treat an SAE) will be recorded.

Study Period	**Screen-ing**	**Treatment Cycle = 21 days**										**EOT**	**Post treatment**			**Notes**
													Safety[2]	**Follow-up[3]**	**Survival**	
Visit Timing[1]/Cycle Number	**-28 to -1**	**1**			**2**		**3**	**4**	**5**	**6-35**	**>36**		**30 Days post last dose**	**Every 6/9/12 Weeks**	**Every 12 Weeks**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 for visit details.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (Days)		**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At D/C**	**+ 7**	**± 7**	**± 14**	
Contact			X													Participants will be contacted on C1D8 to assess for development of early toxicity. If early toxicity is suspected, an unscheduled visit can occur prior to C1D15 if deemed necessary by the investigator.
New Anticancer Therapy Status												X	X	X	X	All anticancer therapy will be recorded until time of death or termination of Survival Follow-up. If a clinic visit is not feasible, follow-up information may be obtained via telephone or e-mail.
Survival Status		←									→				X	Participants may be contacted for survival status at any time during the course of the study.
Treatment Eligibility Assessment (TEA)	X															The investigator must complete the eCRF and provide rationale to document the choice of (or potential treatment with) cisplatin prior to randomization.
Study Intervention – ***Per Randomized Assignment***																
Treatment Randomization		X														Dose within 3 days of randomization.
Lenvatinib Dispensed		X			X		X	X	X	X	X					

Study Period	Screening	Treatment Cycle = 21 days										EOT	Post treatment			Notes
													Safety[2]	Follow-up[3]	Survival	
Visit Timing[1]/Cycle Number	**-28 to -1**	**1**			**2**		**3**	**4**	**5**	**6-35**	**>36**		**30 Days post last dose**	**Every 6/9/12 Weeks**	**Every 12 Weeks**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 for visit details.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (Days)		**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At D/C**	**+ 7**	**± 7**	**± 14**	
Lenvatinib Administration		←									→					Dose of lenvatinib will be administered in the clinic on Day 1 of each cycle and Day 15 of Cycle 1, 0 to 4 hours after completion of pembrolizumab administration and before chemotherapy. Self-administer on all other days.
Pembrolizumab Administration		X			X		X	X	X	X						Administered as the first study intervention on Day 1 of each 21-day cycle.
Carboplatin or Cisplatin Administration		X			X		X	X								
Pemetrexed Administration		X			X		X	X	X	X	X					Pemetrexed should be administered at least 30 minutes prior to carboplatin or cisplatin during those treatment cycles. Premedication should be dosed per the approved product labels.
Clinical Procedures/Assessments																
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Report AEs occurring within 30 days after the last dose of study intervention. Report SAEs occurring within 90 days after the last dose of study intervention, or 30 days after the last dose of study intervention if a new anticancer therapy is initiated, whichever is earlier.

Study Period	**Screen-ing**	**Treatment Cycle = 21 days**										**EOT**	**Post treatment**			**Notes**
													Safety[2]	**Follow-up[3]**	**Survival**	
Visit Timing[1]/Cycle Number	**-28 to -1**	**1**			**2**		**3**	**4**	**5**	**6-35**	**>36**		**30 Days post last dose**	**Every 6/9/12 Weeks**	**Every 12 Weeks**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 for visit details.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (Days)		**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At D/C**	**+ 7**	**± 7**	**± 14**	
Full Physical Examination	X											X				At Screening, perform within 7 days prior to C1D1.
Directed Physical Examination		X		X	X	X	X	X	X	X	X		X			
Height	X															
Vital Signs and Weight	X	X		X	X	X	X	X	X	X	X	X	X			Vital signs must be taken in the clinic. Refer to Section 6.6.1.1 for hypertension management BP monitoring guidelines. D15 visit is mandatory in C1 and C2. During C3 and subsequent cycles, participants may return for the D15 visit if BP monitoring is required as specified in Section 6.6.1.1.

Study Period	Screen-ing	Treatment Cycle = 21 days										EOT	Post treatment			Notes
													Safety[2]	Follow-up[3]	Survival	
Visit Timing[1]/Cycle Number	**-28 to -1**	**1**			**2**		**3**	**4**	**5**	**6-35**	**>36**		**30 Days post last dose**	**Every 6/9/12 Weeks**	**Every 12 Weeks**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 for visit details.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (Days)		**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At D/C**	**+ 7**	**± 7**	**± 14**	
12-Lead ECG with QTc Measurement	X	X			X					X	X	X	X			ECG at Screening , C1D1, C2D1, D1 of every fourth cycle 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 patients (as defined in Section 8.3.3), conduct ECG monitoring every cycle. If lenvatinib/matching placebo is discontinued, ECG is only required at EOT and Safety Follow-up visits.
ECHO/MUGA	X											X				Additional assessments may be performed as clinically indicated.
ECOG Performance Status	X	X			X		X	X	X	X	X	X	X			At Screening, perform within 7 days prior to C1D1 but before randomization.
Brain MRI	X															Required at Screening. Follow-up MRI is required as clinically indicated, and at subsequent suspected CR. If MRI is contraindicated or cannot be performed CT head with contrast is acceptable.

Study Period	Screen-ing	Treatment Cycle = 21 days										EOT	Post treatment			Notes
													Safety[2]	Follow-up[3]	Survival	
Visit Timing[1]/Cycle Number	**-28 to -1**	**1**			**2**		**3**	**4**	**5**	**6-35**	**>36**		**30 Days post last dose**	**Every 6/9/12 Weeks**	**Every 12 Weeks**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 for visit details.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (Days)		**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At D/C**	**+ 7**	**± 7**	**± 14**	
Laboratory Procedures/Assessments: LOCAL																
Serum HCG or urine pregnancy test (WOCBP only)	X				X		X	X	X	X	X	X	X			WOCBP require negative test prior to randomization. If more than 24 hours have elapsed prior to first dose of study intervention, another pregnancy test is required prior to starting study intervention. A serum or urine pregnancy test will be performed per Appendix 2.
Hepatitis B and C Serology	X															Not required unless mandated by local health authorities.
HIV Testing	X															Not required unless mandated by local health authorities.
PT/INR and aPTT/PTT	X															Perform eligibility labs within 10 days prior to C1D1. Additional testing to be conducted as clinically indicated for participants taking anticoagulant therapy.

Study Period	**Screen-ing**	**Treatment Cycle = 21 days**										**EOT**	**Post treatment**			**Notes**
													Safety[2]	**Follow-up[3]**	**Survival**	
Visit Timing[1]/Cycle Number	**-28 to -1**	**1**			**2**		**3**	**4**	**5**	**6-35**	**>36**		**30 Days post last dose**	**Every 6/9/12 Weeks**	**Every 12 Weeks**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 for visit details.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (Days)		**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At D/C**	**+ 7**	**± 7**	**± 14**	
CBC with Differential	X			X	X		X	X	X	X	X	X	X			At Screening, perform within 10 days prior to C1D1. After Cycle 1, may collect up to 3 days prior to dosing.
Chemistry Panel	X			X	X		X	X	X	X	X	X	X			
Thyroid Function (T3, FT4, and TSH)	X				X			X		X	X	X	X			At Screening, C2D1, then every 2 cycles thereafter. Screening samples to be collected within 10 days before first dose. Participants may be dosed in subsequent cycles after C1D1 while thyroid function tests are pending. After C1, collect within 3 days before dosing. May use central laboratory only if local laboratory is not capable.

Study Period	**Screen-ing**	**Treatment Cycle = 21 days**										**EOT**	**Post treatment**			**Notes**
													Safety[2]	**Follow-up[3]**	**Survival**	
Visit Timing[1]/Cycle Number	**-28 to -1**	**1**			**2**		**3**	**4**	**5**	**6-35**	**>36**		**30 Days post last dose**	**Every 6/9/12 Weeks**	**Every 12 Weeks**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 for visit details.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (Days)		**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At D/C**	**+ 7**	**± 7**	**± 14**	
Urinalysis/Urine Dipstick Testing	X			X	X	X	X	X	X	X	X	X	X			Performed locally within 7 days before first dose. After C1, collect within 3 days before dosing. Urinalysis is required at Screening and every 4 cycles. At other time points, either urinalysis or urine dip stick are acceptable. If lenvatinib/ matching placebo is discontinued, urinalysis is required every 4 cycles. For participants with proteinuria >1+ during Screening, refer to Exclusion Criterion 26. For management of proteinuria, refer to Section 6.6.1.2 D15 visit is mandatory in C1 and C2. During C3 and subsequent cycles, participants may return for the D15 visit if monitoring is required as specified above.

Study Period	**Screen-ing**	**Treatment Cycle = 21 days**										**EOT**	**Post treatment**			**Notes**
													Safety[2]	**Follow-up[3]**	**Survival**	
Visit Timing[1]/Cycle Number	**-28 to -1**	**1**			**2**		**3**	**4**	**5**	**6-35**	**>36**		**30 Days post last dose**	**Every 6/9/12 Weeks**	**Every 12 Weeks**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 for visit details.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (Days)		**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At D/C**	**+ 7**	**± 7**	**± 14**	
Laboratory Procedures/Assessments: CENTRAL																
Plasma Sample for Lenvatinib PK		X		X	X											C1D1: 0.5 to 4 and 6 to 10 hours postdose C1D15: predose, and 2 to 12 hours postdose C2D1: predose, 0.5 to 4 and 6 to 10 hours postdose All predose samples should be collected within 2 hours of lenvatinib administration. Postdose samples not needed if lenvatinib administration is skipped.
Serum for Pembrolizumab PK		X			X											Prior to pembrolizumab infusion on C1D1, C2D1, and C8D1.
Antipembrolizumab Antibodies		X			X											
Tumor Tissue Collection																
Newly Obtained/Archival Tissue Sample for Biomarker Analysis	X															May use archival tissue sample that was obtained prior to Screening period as part of the participant's SOC.
EGFR, *ALK*, and *ROS1* Molecular Status	X															Not required for participants with KRAS mutation. May send tumor tissue to central lab for molecular testing if status is unknown and cannot be determined locally.

Study Period	Screening	Treatment Cycle = 21 days										EOT	Post treatment			Notes
													Safety[2]	Follow-up[3]	Survival	
Visit Timing[1]/Cycle Number	**-28 to -1**	**1**			**2**		**3**	**4**	**5**	**6-35**	**>36**		**30 Days post last dose**	**Every 6/9/12 Weeks**	**Every 12 Weeks**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated. Refer to Section 8.11 for visit details.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (Days)		**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At D/C**	**+ 7**	**± 7**	**± 14**	
Efficacy Assessments																
Tumor Imaging and Response Assessment (Thorax, Abdomen, Pelvis)	X	⟷										X		X*		Perform imaging at Screening, 6, 12, and 18 weeks from the day of randomization, then Q9W through Week 54, and Q12W thereafter; ie, 6, 12, 18, 27, 36, 45, 54, 66, 78, 90, etc. weeks from the day of randomization. Schedule should be followed regardless of treatment delays. If imaging was obtained within 4 weeks prior to EOT, scan at EOT is not mandatory. *The visit window at the 6-week time point is + 7 days.

Abbreviations: AE = adverse event; ALK = anaplastic lymphoma kinase; aPTT = activated partial thromboplastin time; BICR = blinded independent central (imaging) review; CBC = complete blood count; CR = complete response; CXDX = Cycle X, Day X; D/C = discontinuation; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EGFR = epidermal growth factor receptor; EORTC = European Organisation for Research and Treatment of Cancer; EOT = end of treatment; ePRO = electronic patient-reported outcome; EQ-5D-5L = EuroQoL 5-dimension, 5-level Questionnaire; FT4 = free thyroxine; hr = hours; HBV/HCV = Hepatitis B/C virus; HCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; ICF = informed consent form; ID = identification; INR = international normalized ratio; IRB/IEC = Institutional Review Board/Independent Ethics Committee; min = minute(s); MRI = magnetic resonance imaging; MUGA = multigated acquisition; NSCLC = non-small cell lung cancer; PD = progressive disease; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; Q = every; QLQ-C30 = Quality of Life Questionnaire Core 30; QLQ-LC13 = Quality of Life Questionnaire and Lung Cancer Module 13; QTc = corrected QT interval; RNA = ribonucleic acid; ROS1 = c-ros oncogene 1; SAE = serious adverse event; SoA = schedule of activities; SOC = standard of care; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating- hormone; W = weeks; WOCBP = woman of childbearing potential; WONCBP = woman of nonchildbearing potential

1. At Screening, visit timing is in relation to the first dose of study intervention.
2. The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study intervention or before initiation of new anticancer therapy, whichever is earlier. If the End of Treatment Visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required.
3. For participants who D/C study intervention for reasons other than BICR-verified PD, follow-up visits to monitor disease status continue until BICR-verified PD or initiation of a new anticancer therapy. Participants who D/C study intervention with BICR-verified PD proceed directly to Survival Follow-up.

1.3.2 Second Course Treatment (Retreatment) - Parts 1 and 2

Study Period	**Treatment Cycle = 21 days**						**EOT**	**Posttreatment**			**Notes**
								Safety[1]	**Follow-up[2]**	**Survival**	
Visit Timing/Cycle Number	**1**	**2**	**3**	**4**	**5**	**≥6**		**30 (+ 7) Days After Last Dose**	**Every 12 Weeks**	**Every 12 Weeks**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated.**
Scheduling Window (Days)	**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At D/C**	**+ 7**	**± 7**	**± 14**	
Administrative and General Procedures											
Inclusion/exclusion Criteria	X										
Prior/Concomitant Medications	X	X	X	X	X	X	X	X			Prior medications taken within 30 days before the first dose of Second Course Treatment and concomitant medications taken during the study and for 30 days after the last dose of Second Course Treatment (or 90 days if used to treat an SAE) will be recorded.
New Anticancer Therapy Status							X	X	X	X	
Survival Status	←	—	—	—	—	—	—	—	—	→	Participants may be contacted for survival status at any time during the course of the study.
Study Intervention – ***Per Randomized Assignment***											
Lenvatinib Dispensed	X	X	X	X	X	X					The decision of whether or not to continue lenvatinib during Second Course will be at the discretion of the investigator if the patient was receiving lenvatinib in First Course. If continued, the dose of lenvatinib will be given in clinic on Day 1 of each SC Cycle, 0 to 4 hours after completion of pembrolizumab administration; it will be self-administered on all other days. Treatment with lenvatinib will continue until meeting at least 1 of the D/C criteria listed in Section 7.1.
Lenvatinib Administration for patients who received lenvatinib in First Course	←	—	—	—	—	→					

Study Period	Treatment Cycle = 21 days						EOT	Posttreatment			Notes
								Safety[1]	Follow-up[2]	Survival	
Visit Timing/Cycle Number	**1**	**2**	**3**	**4**	**5**	**≥6**		**30 (+ 7) Days After Last Dose**	**Every 12 Weeks**	**Every 12 Weeks**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated.**
Scheduling Window (Days)	**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At D/C**	**+ 7**	**± 7**	**± 14**	
Pembrolizumab Administration	X	X	X	X	X	X					Participants who are eligible for Second Course may receive up to an additional 17 cycles of treatment with pembrolizumab. Pembrolizumab will be administered as the first study intervention on Day 1 of each 21-day SC Cycle.
Clinical Procedures/Assessments											
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X		Report AEs occurring within 30 days after the last dose of study intervention. Report SAEs occurring within 90 days after the last dose of study intervention, or 30 days after the last dose of study intervention if a new anticancer therapy is initiated, whichever is earlier.
Full Physical Examination	X						X				
Directed Physical Examination		X	X	X	X	X		X			
Vital Signs, Weight	X	X	X	X	X	X	X	X			Vital signs must be taken in the clinic. Refer to Section 6.6.1.1 for hypertension management BP monitoring guidelines. Participants may return for the D15 visit if BP monitoring is required as specified in Section 6.6.1.1.
12-Lead ECG with QTc Measurement	X*				X	X*	X	X			If lenvatinib/ matching placebo is discontinued, ECG is only required at EOT and Safety Follow-up visits. *Every fourth cycle beginning with Cycle 5 (eg, C5, C9, C13, etc.).
ECOG Performance Status	X	X	X	X	X	X	X	X			Perform within 7 days prior to SC Cycle 1.

Study Period	Treatment Cycle = 21 days						EOT	Posttreatment			Notes
								Safety[1]	Follow-up[2]	Survival	
Visit Timing/Cycle Number	**1**	**2**	**3**	**4**	**5**	**≥6**		**30 (+ 7) Days After Last Dose**	**Every 12 Weeks**	**Every 12 Weeks**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated.**
Scheduling Window (Days)	**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At D/C**	**+ 7**	**± 7**	**± 14**	
Laboratory Procedures/Assessments: LOCAL											
Serum HCG or urine pregnancy test (WOCBP only)	X	X	X	X	X	X	X	X			WOCBP require negative test prior to randomization. If more than 24 hours have elapsed prior to first dose of study intervention in SC C1, another pregnancy test is required prior to starting study intervention. A serum or urine pregnancy test will be performed per Appendix 2.
PT/INR and aPTT/PTT	X										Additional testing to be conducted as clinically indicated for participants taking anticoagulant therapy.
CBC with Differential	X	X	X	X	X	X	X	X			Perform within 10 days prior to SC Cycle 1. After SC Cycle 1, may collect up to 3 days prior to dosing.
Chemistry Panel	X	X	X	X	X	X	X	X			
Thyroid Function (T3, FT4, and TSH)	X*		X		X*		X	X			*Thyroid function tests will be performed at C1 and every 2 cycles thereafter. Perform within 10 days before SC C1. After SC C1, collect within 3 days before dosing. Participants may be dosed in subsequent cycles after SC C1 while thyroid function tests are pending. May use central laboratory only if local laboratory is not capable.

Study Period	Treatment Cycle = 21 days						EOT	Posttreatment			Notes
								Safety[1]	Follow-up[2]	Survival	
Visit Timing/Cycle Number	**1**	**2**	**3**	**4**	**5**	**≥6**		**30 (+ 7) Days After Last Dose**	**Every 12 Weeks**	**Every 12 Weeks**	**All procedures and assessments are to be performed prior to administration of study intervention unless otherwise indicated.**
Scheduling Window (Days)	**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At D/C**	**+ 7**	**± 7**	**± 14**	
Urinalysis/Urine Dipstick Testing	X	X	X	X	X	X	X	X			Performed locally within 7 days before SC Cycle 1. After SC Cycle 1, collect within 3 days before dosing. If lenvatinib/ matching placebo is discontinued, urinalysis is required every 4 cycles. Repeat testing for participants with proteinuria ≥2+ should be performed as clinically indicated until the results have been 1+ or negative for 2 consecutive treatment cycles.
Efficacy Assessments											
Tumor Imaging and Response Assessment (Thorax, Abdomen, Pelvis)	X				X	X	X		X		SC baseline imaging within 30 days prior to SC Cycle 1. Perform imaging Q12W (± 7 days) from SC Cycle 1 (ie, 12, 24, 36, 48, etc. weeks after SC Cycle 1). Schedule should be followed regardless of treatment delays. If imaging was obtained within 4 weeks prior to EOT, scan at EOT is not mandatory.

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; HCG = human chorionic gonadotropin; CBC = complete blood count; D/C = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment； FT4 = free thyroxine; INR = international normalized ratio; PD = progressive disease; PT = prothrombin time; PTT = partial thromboplastin time; Q = every; QTc = corrected QT interval; SAE = serious adverse event; SC = Second Course; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; W = weeks; WOCBP = woman of childbearing potential

1. The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study intervention or before initiation of new anticancer therapy, whichever is earlier. If the End of Treatment Visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required.
2. For participants who D/C study intervention for reasons other than BICR-verified PD, follow-up visits to monitor disease status continue until BICR-verified PD or initiation of a new anticancer therapy. Participants who D/C study intervention with BICR-verified PD proceed directly to Survival Follow-up.

2 INTRODUCTION

2.1 Study Rationale

The standard of care (SOC) for metastatic non-small cell lung cancer (NSCLC) has changed in recent years with the development of immunotherapeutic agents. Prior to the advent of immune checkpoint inhibitors, platinum-based doublet chemotherapy was considered SOC for patients with newly diagnosed, metastatic NSCLC. Despite the benefits of chemotherapy in prolonging survival in this group of patients, the outcome remains dismal. The expected median survival is about 1 year, and the 5-year survival rate is less than 5% [Cronin, K. A., et al 2018]. The arrival of immune checkpoint blockage, particularly the programmed cell death protein 1 (PD-1) inhibitors, has changed the treatment paradigm in metastatic lung cancer. The United States (US) Food and Drug Administration (FDA) has approved pembrolizumab as the first anti-PD-1 receptor antibody for the treatment of metastatic nonsquamous NSCLC either as monotherapy in tumors with high programmed death ligand 1 (PD-L1) expression (tumor proportion score [TPS] ≥50%), or in combination with chemotherapy for all nonsquamous NSCLC regardless of PD-L1 expression. With pembrolizumab treatment, the median overall survival (OS) in this group is >30 months, with a 1-year OS of ~ 70%, compared to a 1-year OS of ~ 50% for patients receiving chemotherapy without pembrolizumab [Gandhi, L., et al 2018].

Despite the improvement in OS in patients with metastatic NSCLC treated with checkpoint inhibitors, a significant portion of these patients will die of their disease. As such, new therapeutics, as well as novel combinations, are needed to improve outcomes. The present study is designed to further evaluate the safety and efficacy of combination therapy with lenvatinib (also known as E7080 or MK-7902), hereafter referred to as lenvatinib, pembrolizumab, and SOC chemotherapy as a first-line (1L) treatment in adult participants with metastatic NSCLC.

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 IB.

Lenvatinib (also known as E7080 or MK-7902; hereafter referred to as lenvatinib) is a multiple receptor tyrosine kinase inhibitor (RTKi) with a potentially differentiated profile. It inhibits the 3 main vascular endothelial growth factor (VEGF) receptors (VEGFRs), VEGFR1, VEGFR2, and VEGFR3, as well as fibroblast growth factor receptors (FGFRs), FGFR1, FGFR2, FGFR3, and FGFR4, platelet-derived growth factor receptor (PDGFR) α, c-kit, and the *RET* proto-oncogene, which play roles in tumor angiogenesis, tumor progression, and modification of tumor immunity.

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

2.2.1 Pharmaceutical and Therapeutic Background

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].

2.2.1.1 Lenvatinib

Angiogenesis, the formation of new blood vessels from a pre-existing vascular network, is essential for tumor growth and metastasis. VEGF and its family of receptors (VEGRs 1-3) play a major role in tumor angiogenesis [Ferrara, N., et al 2003] [Ellis, L. M. 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.

Co-crystal structural analysis demonstrated that lenvatinib has a distinct mode of interaction with VEGFR2 or FGFR1, termed Type V, while most of the known kinase inhibitors on the market are categorized as Type I or II [Okamoto, K., et al 2015]. Lenvatinib binds to ATP-binding sites and neighboring allosteric regions in the kinase domain adopting the DFG-in conformation. Most of the known kinase inhibitors are categorized as Type I, binding these kinases in the DFG-in configuration and only binding to the ATP-binding site, or Type II binding to the kinase in the DFG-out conformation and binding to both the ATP-binding site and the neighboring regions.

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 exhibited antitumor activity against various human tumor

xenografts in athymic mice including 5 types of thyroid carcinomas (differentiated [papillary and follicular], anaplastic, squamous, and medullary thyroid carcinomas), 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.

2.2.1.2 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) [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008].

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. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as 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 NSCLC.

2.2.1.3 Lung Cancer: Epidemiology and Current Therapeutic Options

The global incidence of lung cancer was 1.8 million in 2012, resulting in an estimated 1.6 million deaths [World Health Organization 2012]. In the United States, the 2018 estimated incidence of new diagnoses was 234,030, and the estimated number of deaths was 154,050 [National Cancer Institute 2018]. NSCLC represents approximately 80% to 85% of all lung cancers. Of the patients with NSCLC, tumor histology is approximately 40% to 60% adenocarcinoma, 10% to 15% squamous, 5% neuroendocrine, and the rest, "not otherwise specified" [Sulpher, J. A., et al 2013].

Approximately 70% of patients with NSCLC have advanced disease not amenable to surgical resection at the time of diagnosis. From 2006 to 2012, the overall 5-year relative survival rate for lung cancer was 17.7% in the United States. Five-year relative survival rates were 55% for localized, 28% for regional, 4.3% for distant, and 7.4% for unstaged [National Comprehensive Cancer Network 2017].

In the Phase 3 study KEYNOTE-024, pembrolizumab, a PD-1 inhibitor, showed statistically significant increases in OS and progression-free survival (PFS) compared to SOC platinum-based chemotherapy for treatment-naïve participants with metastatic NSCLC whose tumors expressed high levels of PD-L1 (TPS ≥50%) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations, leading to regulatory approval for this indication in the US and other countries around the world. Approximately 30% of patients with newly diagnosed, advanced NSCLC highly express PD-L1 to a TPS ≥50% [Reck, M., et al 2016].

In the Phase 2 study KEYNOTE-021 Cohort G, pembrolizumab plus pemetrexed and carboplatin showed statistically significant increases in objective response rate ([ORR]; 55% vs. 29%) and PFS (8.9 vs. 13.0 months, HR 0.53 [95% confidence interval [CI] 0.31 to 0.91]) compared to pemetrexed and carboplatin alone in participants with nonsquamous advanced NSCLC, regardless of PD-L1 status [Langer, C. J., et al 2016]. Moreover, a recent update of data from KEYNOTE-021 showed that an OS benefit has also been seen when pembrolizumab is added to chemotherapy (hazard ratio [HR] 0.59; 95% CI 0.34 to 1.05; p=0.03) [Borghaei, H., et al 2017]. These findings were confirmed in the Phase 3 randomized, double-blinded KEYNOTE-189 study of pemetrexed and a platinum-based chemotherapy with or without pembrolizumab in 1L, metastatic, nonsquamous NSCLC. KEYNOTE-189 showed that treatment with pembrolizumab plus pemetrexed and platinum-based chemotherapy (carboplatin or cisplatin) significantly prolonged OS (HR 0.49; 95% CI 0.38 to 0.64; $p<0.001$) and PFS (HR 0.52; 95% CI 0.43 to 0.64; $p<0.001$) compared with SOC chemotherapy. These results established pembrolizumab plus chemotherapy as an efficacious option for 1L treatment in patients with nonsquamous NSCLC [Gandhi, L., et al 2018].

Taken together, strong efficacy data from randomized KEYNOTE studies have established an important role for pembrolizumab either as monotherapy or in combination with chemotherapy in patients with NSCLC.

2.2.1.4 Lenvatinib Activity in Non-small Cell Cancer

Lenvatinib has been studied in advanced NSCLC. As a single agent, a randomized Phase 2 study (E7080703) of lenvatinib versus placebo was conducted in 135 participants with locally advanced or metastatic nonsquamous NSCLC who had failed to respond to at least 2 systemic anticancer regimens. Eighty-nine participants received 24 mg lenvatinib qd and 46 received placebo; all participants received best supportive care in addition to study intervention. Median OS was 38.4 weeks for lenvatinib and 24.1 weeks for placebo, median PFS was 20.9 weeks for lenvatinib and 7.9 weeks for placebo, ORR was 10.1% for lenvatinib and 2.2% for placebo, and DCR was 42.7% for lenvatinib and 19.6% for placebo. The toxicities were manageable. Grade 3/4 AEs occurred in 69% of lenvatinib recipients, and in

50% of placebo recipients. Grade 3/4 AEs were dyspnea and pneumonia in both treatment groups, as well as hypertension in the lenvatinib group [Havel, L., et al 2014].

In a Phase 1/2 study (Study E7080-J081-110), lenvatinib at 4 mg BID was examined in combination with carboplatin AUC 6 and paclitaxel 200 mg/m^2 in Japanese participants with NSCLC. The ORR was 61% (95% CI: 41% to 79%) and was composed of 1 CR and 16 PRs. The median PFS was reported as 9 months. In this study, the most frequently reported Grade 3 and Grade 4 toxicities were neutropenia (95%), leukopenia (50%), hypertension (36%), thrombocytopenia (27%), and febrile neutropenia (23%)[Nishio, M., et al 2013]. In the Four-Arm Cooperative Group Study (FACS), 4 common platinum doublets as first-line intervention were compared in Japanese participants with NSCLC. The Grade 3 and Grade 4 events observed in the carboplatin and paclitaxel arm were neutropenia (88%), febrile neutropenia (18%), and thrombocytopenia (11%). These data suggest that the addition of lenvatinib potentially leads to enhanced efficacy without significant enhancement of the hematologic toxicities from chemotherapy [Ohe, Y., et al 2007].

2.2.1.5 Scientific Rationale for the Combination of Lenvatinib and Pembrolizumab

Early studies have shown that lenvatinib has antitumor activity in many solid tumors. LENVIMA® (lenvatinib) is a kinase inhibitor that is indicated for differentiated thyroid cancer (DTC) as a single agent for patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory DTC and for RCC in combination with everolimus for patients with advanced RCC following one prior antiangiogenic therapy [U.S. Prescribing Information 2018]. In both tumor types, lenvatinib statistically significantly prolonged PFS. Lenvatinib monotherapy is also approved for the first-line treatment of patients with unresectable HCC.

In preclinical models, lenvatinib decreased the tumor-associated macrophage (TAM) population, which is known as an immune regulator in the tumor microenvironment. By decreasing TAMs, expression levels of cytokines and immune-regulating receptors were changed to increase immune activation. The immune-modulating effect of lenvatinib may result in a potent combination effect with PD-1/PD-L1 signal inhibitors. The effect of combining lenvatinib with anti-PD-1/PD-L1 inhibitors has been investigated in the CT26 colorectal cancer syngeneic model (anti-PD-L1 inhibitor) and the LL/2 lung cancer syngeneic model (anti-PD-1 mAb). Combination treatment with lenvatinib and either an anti-PD-1 or anti-PD-L1 inhibitor showed significant and superior antitumor effects compared with either compound alone, in these 2 syngeneic models [Kato, Y., et al 2015].

For this reason, an open-label, Phase 1b/2 study (Study E7080 A001 111 [Study 111]) to assess the safety and preliminary antitumor activity of the combination of lenvatinib plus pembrolizumab in participants with selected solid tumors was initiated. Phase 1b of this study determined the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of lenvatinib as 20 mg 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 (NSCLC, renal cell carcinoma [RCC], endometrial cancer, urothelial carcinoma, melanoma, and squamous cell carcinoma of the head and neck).

2.2.2 Preclinical and Clinical Studies

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

2.2.3 Ongoing Clinical Studies of Lenvatinib and Pembrolizumab

Pembrolizumab is under evaluation in patients with NSCLC as monotherapy and in combination with chemotherapy, immunotherapy, and targeted therapies. Lenvatinib is being studied in patients with different types of solid tumors, including NSCLC, and in combination with other therapies, including PD-1-targeted therapies. A full list of ongoing studies can be found in the respective IBs of pembrolizumab [IB Edition 16 2018] and lenvatinib [IB Edition 15-Eisai 2018]. Details of the ongoing study 111/KEYNOTE-146 are outlined below.

Study 111/KEYNOTE-146

Study 111/KEYNOTE-146, is a multicenter, open-label, Phase 1b/2 clinical study to evaluate the efficacy and safety of lenvatinib in combination with pembrolizumab. The primary objective of the Phase 1b portion of the study is to determine the MTD in participants with unresectable solid tumors (endometrial cancer, melanoma, NSCLC, RCC, squamous cell carcinoma of the head and neck, and urothelial cancer) who have progressed after treatment with approved therapies or for which there are no standard effective therapies available. The primary endpoint of the initial part of Phase 2 is ORR after 24 weeks of treatment, with select secondary endpoints, including ORR, disease control rate, PFS, and duration of response (DOR).

As of the data cutoff of 01-DEC-2017, 20 participants with NSCLC were enrolled (data on file). Of the enrolled participants, 9 (45%) were PD-L1(+) (TPS ≥1%), 5 (25%) were PD-L1(−), and 6 (30%) were not tested; 3 (15%) were treatment-naïve; and 6 (30%), 9 (45%), and 2 (10%) had 1, 2, and ≥3 prior lines of systemic therapy, respectively. The primary endpoint of ORR at Week 24 was 30.0% (95% CI, 11.9% to 54.3%). Grade 3 and 4 treatment-related AEs occurred in 11 participants (55%) and 1 participant (5%), respectively (ie, increased aspartate aminotransferase [AST]). There was 1 fatal treatment-related AE (exsanguination that was deemed “possibly related” to study intervention). The most common Grade 3 treatment-related AEs were hypertension (30% [6 of 20 participants]) and fatigue, diarrhea, and hyponatremia (15% [3 of 20 subjects]). These findings indicate that the combination of lenvatinib with pembrolizumab shows promising clinical activity with a manageable safety profile in previously treated patients with metastatic NSCLC who were not preselected for PD-L1 status.

2.2.4 Information on Other Study-related Therapy

Study participants will receive concomitant chemotherapy with either carboplatin or cisplatin and pemetrexed as per their product labels. Refer to their respective package inserts for more information.

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.

While there are options for patients with metastatic NSCLC, a significant percentage of these patients will die from their cancer. As such, there is a continual need for novel therapies in this setting. Moreover, as discussed in the previous section, both lenvatinib and pembrolizumab combination therapy alone and given concomitantly with chemotherapy have shown activity in NSCLC. The most common Grade 3 treatment-emergent AEs were hypertension (24%), fatigue (14%), diarrhea (14%), proteinuria (10%), and arthralgia (10%) (Data on file). Toxicities were manageable with dose interruption and/or modification and no new safety signals were found. 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 ICF documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

The objectives of the study are as follows, in participants with nonsquamous non-small cell lung cancer (NSCLC), who are at least 18 years of age:

Throughout this protocol, the term RECIST 1.1 refers to the modification of RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Refer to Section 4.2.1.1.3 for further details.

Objectives	Endpoints
Primary	
• Part 1: To evaluate the safety and tolerability of treatment with lenvatinib + platinum doublet chemotherapy + pembrolizumab.	• Dose-limiting toxicities (DLTs), adverse events (AEs) and study intervention discontinuations due to AEs.
• Part 2: To compare progression free survival (PFS) as assessed by blinded independent central review (BICR) according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) for lenvatinib + platinum doublet chemotherapy + pembrolizumab versus matching placebo + platinum doublet chemotherapy + pembrolizumab. • Hypothesis (H1): The combination of lenvatinib +platinum doublet chemotherapy + pembrolizumab prolongs PFS per RECIST 1.1 by BICR compared to matching placebo + platinum doublet chemotherapy + pembrolizumab.	• PFS, defined as the time from randomization to the date of the first documentation of disease progression or death from any cause, whichever is earlier.
• Part 2: To compare overall survival (OS) for the combinations of lenvatinib + platinum doublet chemotherapy + pembrolizumab versus matching placebo + platinum doublet chemotherapy + pembrolizumab. • Hypothesis (H2): The combination of lenvatinib + platinum doublet chemotherapy + pembrolizumab prolongs OS compared to matching placebo + platinum doublet chemotherapy + pembrolizumab.	• OS, defined as the time from randomization to the date of death from any cause.

Objectives	Endpoints
Secondary	
• Part 2: To compare objective response rate (ORR) as assessed by BICR according to RECIST 1.1 for the combinations of lenvatinib + platinum doublet chemotherapy + pembrolizumab versus matching placebo + platinum doublet chemotherapy + pembrolizumab. • Hypothesis (H3): The combination of lenvatinib + platinum doublet chemotherapy + pembrolizumab has superior ORR per RECIST 1.1 by BICR compared to matching placebo + platinum doublet chemotherapy + pembrolizumab.	• Objective response (OR), defined as a confirmed complete response (CR) or partial response (PR).
• Part 2: To evaluate duration of response (DOR) per RECIST 1.1 by BICR for the combinations of lenvatinib + platinum doublet chemotherapy + pembrolizumab and matching placebo + platinum doublet chemotherapy + pembrolizumab.	• DOR, defined as the time from the first documented evidence of CR or PR until disease progression or death due to any cause (whichever is earlier), for participants who demonstrate a confirmed CR or PR.
• Part 2: To evaluate the safety and tolerability for the combinations of lenvatinib + platinum doublet chemotherapy + pembrolizumab and matching placebo + platinum doublet chemotherapy + pembrolizumab.	• Adverse events (AEs) and study intervention discontinuations due to AEs.
• Part 2: To evaluate the mean change from baseline in global health status/quality of life (QoL), cough, chest pain, dyspnea, and physical functioning for the combinations of lenvatinib + platinum doublet chemotherapy + pembrolizumab and matching placebo + platinum doublet chemotherapy + pembrolizumab.	• Change from baseline for the following patient-reported outcomes (PRO) scales/items: global health status/QoL (EORTC QLQ-C30 Items 29 and 30), cough (EORTC QLQ-LC13 Item 31), chest pain (EORTC QLQ-LC13 Item 40), dyspnea (EORTC QLQ-C30 Item 8), and physical functioning (EORTC QLQ-C30 Items 1 through 5).

Objectives	Endpoints
• Part 2: To evaluate the time to true deterioration (TTD) in global health status/QoL, cough, chest pain, dyspnea, and physical functioning for the combinations of lenvatinib + platinum doublet chemotherapy + pembrolizumab and matching placebo + platinum doublet chemotherapy + pembrolizumab.	• TTD, defined as the time from baseline to the first onset of a ≥10-point deterioration from baseline with confirmation by the subsequent visit of a ≥10-point deterioration from baseline in global health status/QoL (EORTC QLQ-C30 Items 29 and 30), cough (EORTC QLQ-LC13 Item 31), chest pain (EORTC QLQ-LC13 Item 40), dyspnea (EORTC QLQ-C30 Item 8), and physical functioning (EORTC QLQ-C30 Items 1 through 5). • TTD in the composite endpoint (combination of cough [QLQ-LC13 item 31], chest pain [QLQ-LC13 item 40], or dyspnea [QLQ-C30 item 8]) defined as the time to first onset of a ≥10-point deterioration from baseline in any one of 3 scale items with confirmation by the subsequent visit of a ≥10-point deterioration from baseline in the same scale as the first onset.
Tertiary/Exploratory	
• Part 2: To evaluate the pharmacokinetics (PK) of lenvatinib when co-administered with pembrolizumab following treatment with lenvatinib + platinum doublet chemotherapy + pembrolizumab.	• Plasma concentration of lenvatinib versus time.
• Part 2: To evaluate and compare participants' health status as assessed by the 5-level version of the European Quality of Life (EuroQoL) 5-dimension Questionnaire (EQ-5D-5L) to generate utility scores for use in economic models.	• Health utilities assessed using the EQ-5D-5L.

Objectives	Endpoints
• Part 2: To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, and/or the mechanism of action of pembrolizumab and lenvatinib in all participants.	• Molecular (genomic, metabolic, and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, randomized, double-blind, active-control with placebo, parallel-group, multisite study of lenvatinib versus matching placebo in combination with pembrolizumab and platinum doublet chemotherapy in participants with treatment-naïve metastatic nonsquamous NSCLC. Eligible participants will have measurable disease based on RECIST 1.1, an ECOG performance status of 0 or 1, and a cancer that is *EGFR*, *ALK*, and *ROS proto-oncogene 1* (*ROS1*) negative.

Currently there is no data available examining the safety profile of lenvatinib with pembrolizumab and chemotherapy. As such, this study will include an open-label safety run-in (Part 1). In Part 1, approximately 12 participants will be treated with lenvatinib in combination with pembrolizumab and platinum doublet chemotherapy to ensure that at least 6 participants will be treated with lenvatinib in combination with pembrolizumab, carboplatin, and pemetrexed, and at least 6 participants will be treated with lenvatinib in combination with pembrolizumab, cisplatin, and pemetrexed. Participants will be closely followed for unacceptable toxicities for 21 days after the first dose of study intervention (the dose-limiting toxicity [DLT] evaluation period) for occurrence of specific AEs that are deemed dose-limiting according to Table 1. If after all Part 1 participants complete the 21-day DLT period, less than 3 DLTs in 6 participants in each platinum-containing arm have occurred, enrollment to Part 2 will begin without delay. If 3 or more DLTs occur in 6 participants in each platinum-containing arm during this safety run-in, enrollment to Part 2 may be delayed to further examine safety data and consider study design changes. Participants in Part 1 will continue to receive study intervention and be followed in the posttreatment period as applicable. Safety data from this population will be reported separately from data in the blinded Phase 3 portion of the study.

Table 1 Dose-limiting Toxicities

Toxicity Category	Toxicity CTCAE Grade
Hematologic	• Grade 4 neutropenia lasting for ≥7 days • Grade 3 or Grade 4 febrile neutropenia[a] • Thrombocytopenia <25,000/mm^3 associated with bleeding and/or which requires platelet transfusion

Other nonhematologic toxicity	• Any other Grade 4 or a Grade 5 toxicity
	• Grade 3 toxicities lasting >3 days excluding:
	  ○ Nausea, vomiting, and diarrhea controlled by medical intervention within 72 hours
	  ○ Grade 3 rash in the absence of desquamation, no mucosal involvement, does not require steroids, and resolves to Grade 1 by the next scheduled dose of pembrolizumab
	• Grade 3 hypertension not able to be controlled by medication
	• Grade 3 or above gastrointestinal perforation
	• Grade 3 or above wound dehiscence requiring medical or surgical intervention
	• Any grade thromboembolic event

	Any Grade 3 nonhematologic laboratory value if:
	  ○ Medical intervention is required to treat the participant, or
	  ○ The abnormality leads to hospitalization

Abbreviations: ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events v4.0.
a Febrile neutropenia Grade 3 or Grade 4
- ○ Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3ºC (101ºF) or a sustained temperature of ≥38ºC (100.4ºF) for more than 1 hour.
- ○ Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3ºC (101ºF) or a sustained temperature of ≥38ºC (100.4ºF) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.

In Part 2, participants will be randomized 1:1 to Arm 1 (lenvatinib + pembrolizumab + platinum doublet chemotherapy) or Arm 2 (matching placebo + pembrolizumab + platinum doublet chemotherapy). Randomization will be stratified by PD-L1 TPS (<50% vs. ≥50%), geographical site (East Asian vs. non-East Asian), and ECOG performance status at Screening (0 vs. 1). The planned sample size is approximately 714 participants with approximately 357 participants in each treatment arm.

The study design is depicted in Figure 1.

Study interventions include oral lenvatinib, 8 mg qd (Arm 1) or matching placebo (Arm 2), and pembrolizumab, 200 mg, carboplatin (AUC 5 mg/mL/min) or cisplatin (75 mg/m^2), and pemetrexed, 500 mg/m^2 all given by intravenous (IV) infusion on Day 1 of a 21-day cycle. Lenvatinib/matching placebo, pembrolizumab, carboplatin/cisplatin, and pemetrexed combination treatment will be given for up to the first 4 cycles, after which participants may receive maintenance treatment with lenvatinib/matching placebo, pembrolizumab, and pemetrexed. Pembrolizumab may be given for up to a total of 35 cycles; there is no treatment duration limit for lenvatinib/matching placebo or pemetrexed. The study has no planned treatment cross-over.

Participants will be evaluated with radiographic imaging to assess response to treatment 6 weeks, 12 weeks, and 18 weeks from the day of randomization, then every 9 weeks through Week 54, and subsequently every 12 weeks until disease progression is documented radiographically per RECIST 1.1 and verified by BICR, initiating a new anticancer therapy, participant withdrawal of consent, pregnancy, becoming lost to follow-up, death, or the end of the study, whichever is earlier.

All imaging obtained on study will be submitted to the imaging vendor for BICR, which will assess the images using RECIST 1.1 (see Section 8.2.1.5) for determination of PFS, ORR, and DOR. Initial tumor imaging showing site-assessed progressive disease (PD) should be submitted immediately for verification by BICR before treatment discontinuation. Treatment-based decisions may use site-assessed iRECIST as described in Section 8.2.1.6, which allows participants with initial site-assessed PD to continue treatment until PD is confirmed by the site 4 to 8 weeks later.

Adverse event monitoring will be ongoing throughout the study and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

An external Data Monitoring Committee (DMC) will evaluate the safety, tolerability, and efficacy of study intervention. The first DMC review will be triggered once at least 10 participants are treated with at least 2 cycles of each of the following regimens: (i) lenvatinib, pembrolizumab, carboplatin, pemetrexed; (ii) placebo, pembrolizumab, carboplatin, pemetrexed; (iii) lenvatinib, pembrolizumab, cisplatin, pemetrexed; and (iv) placebo, pembrolizumab, cisplatin, pemetrexed. Refer to Section 10.1.4 and the DMC Charter for further details.

Study interventions will continue until reaching a discontinuation criterion (Section 7.1), examples of which include disease progression which is radiographically documented and verified by BICR per RECIST 1.1, and only when clinically appropriate, confirmed by the site per iRECIST; unacceptable toxicity; intercurrent illness that prevents further administration of treatment; investigator's decision to withdraw treatment; participant withdrawal of consent; pregnancy; noncompliance with study intervention or procedure requirements; administrative reasons requiring cessation of treatment; or, for carboplatin, cisplatin, and pembrolizumab ONLY, treatment completion (4 cycles of carboplatin or cisplatin/35 cycles of pembrolizumab). There is no treatment duration limit for lenvatinib/matching placebo or pemetrexed.

Participants treated with pembrolizumab who complete 35 cycles of treatment with stable disease (SD) or better or participants who attain an investigator-determined CR and have received at least 8 cycles of pembrolizumab may be eligible for retreatment with up to an additional 17 cycles (approximately 1 year) of pembrolizumab if they experience radiographic disease progression after stopping treatment in the initial treatment phase. This retreatment is termed Second Course Treatment and is only available if the study remains open and the participant meets the criteria listed in Section 7.1.1. Participants will also continue treatment with lenvatinib/placebo at the discretion of the investigator until meeting one of the criteria for treatment discontinuation. Responses or events of progression that

occur during Second Course Treatment will not be counted towards the ORR and PFS endpoints in this study.

The study will be conducted in conformance with Good Clinical Practices (GCP).

Extension Study in China

Approximately 200 participants in China will be randomized overall in the global study and the extension study. After enrollment of the global study is closed, participants in China will continue to be enrolled and randomized in a 1:1 ratio in an extension study designed to meet local regulatory requirements. The extension study will be identical to the global study (eg, double-blinded, with identical inclusion and exclusion criteria, study endpoints, primary and secondary objectives, and study procedures), with the exception of an additional supplemental statistical analysis plan (sSAP) for participants enrolled in China. Details of the analysis will be provided in the separate China-specific sSAP document.

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. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

Further improvements can be made on the therapeutic options available for patients with previously untreated metastatic nonsquamous NSCLC, notwithstanding the progress made with the use of molecularly targeted agents in patients with actionable mutations and with the use of the use of the anti-PD1/anti-PD-L1 antibodies to inhibit suppression of the immune system, which have begun to change outcomes in this patient population.

Pembrolizumab, in particular, has led to a paradigm shift from standard platinum-based doublets utilizing both monotherapy and combination approaches in the first-line treatment of NSCLC. KEYNOTE-024 and KEYNOTE-042 showed that pembrolizumab monotherapy leads to a statistically significant OS benefit in participants with PD-L1-positive metastatic NSCLC compared with chemotherapy, including in participants with squamous histology. However, about 30% of patients with NSCLC have tumors that do not express PD-L1.

Therapeutic approaches to expand on the efficacy of pembrolizumab monotherapy have led to combination strategies with chemotherapy. The efficacy of the combination of pembrolizumab with chemotherapy is expected to be at least additive, and possibly synergistic, due to the immunomodulatory effects of pembrolizumab and induction of PD-L1 expression by cytotoxic chemotherapeutics. Chemotherapy has been shown to augment the antitumor immune response by inducing immunogenic cell death, enhancing the maturation and activation of dendritic cells, increasing T-cell penetrance and function in the tumor, improving the presentation of tumor antigens, and eliminating immunosuppressive cells (T-regulatory cells, myeloid derived suppressor cells, and M2 macrophages) [Apetoh, L., et al 2015].

KEYNOTE-189 demonstrated that treatment with pembrolizumab in combination with pemetrexed/platinum chemotherapy (cisplatin or carboplatin) provided a clinically meaningful and significant improvement in OS [OS HR 0.49; $p<0.00001$; median OS not reached vs. 11.3 months], PFS [PFS HR of 0.52; $p<0.00001$; median PFS 8.8 months vs. 4.9 months] and ORR [47.6% vs. 18.9%; $p<0.0001$] for previously untreated patients with metastatic nonsquamous NSCLC. Importantly, all subgroups benefited from pembrolizumab in combination with pemetrexed and platinum-based chemotherapy, including patients whose tumors did not express PD-L1; therefore, extending the benefit of pembrolizumab to those with PD-L1 negative tumors.

A potential opportunity to improve upon the current therapeutic strategy in nonsquamous NSCLC is by adding an RTKi to pembrolizumab in the maintenance setting. This two-part Phase 3 study is being conducted to evaluate the efficacy and safety of lenvatinib versus matching placebo in combination with pembrolizumab and platinum doublet chemotherapy in participants with treatment-naïve metastatic nonsquamous NSCLC. If the study shows acceptable safety and efficacy profiles with this combination of experimental intervention + SOC and improves outcomes, the study could support the regulatory approval of pembrolizumab + lenvatinib + SOC in patients with metastatic NSCLC.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

4.2.1.1.1 Primary Efficacy Endpoints

This study will use PFS based on RECIST 1.1 criteria adjusted to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by BICR as the primary endpoint and [OS/ORR] as the secondary endpoint. Progression-free survival and ORR are acceptable measures 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 and ORR are typically considered acceptable by regulatory authorities. Images will be read by a central imaging vendor blinded to treatment assignment to minimize bias in the response assessments. In addition, the final determination of radiologic progression will be based on the central assessment of progression, rather than a local site investigator/radiology assessment. Real time determination of radiologic progression as determined by central review will be communicated to the site.

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

For additional details about assessing efficacy endpoints using RECIST 1.1 and iRECIST, see Appendix 6.

4.2.1.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study are ORR and DOR based on RECIST 1.1 and assessed by BICR; both are accepted by regulatory authorities and the oncology community.

4.2.1.1.3 RECIST 1.1

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

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

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen following 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 pseudo-progression. 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 assessment has been developed and published by the RECIST Working Group, with input from leading experts from industry and academia, along with participation from the US Food and Drug Administration and the European Medicines Agency [Seymour, L., et al 2017]. 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 may be performed to confirm radiographic progression. iRECIST will be used by investigators to assess tumor response and progression and make treatment decisions as well as for exploratory efficacy analyses where specified.

4.2.1.2 Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of,

causality, and outcome of AEs/serious adverse events (SAEs); and changes in vital signs and laboratory values. Adverse events will be assessed as defined by CTCAE, Version 4.0.

4.2.1.3 Rationale for Patient-Reported Outcomes

Assessment of symptoms is considered clinically important and accepted by health authorities. Participants will provide information regarding their HRQoL via the following assessment tools: EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D. These measures are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.1.3.1 EORTC QLQ-C30

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

4.2.1.3.2 EORTC QLQ-LC13

The EORTC Quality of Life Questionnaire and Lung Cancer Module 13 (QLQ-LC13), a supplemental lung cancer-specific module used in combination with QLQ-C30, is composed of multi-item and single-item measures of lung cancer-associated symptoms (cough, hemoptysis, dyspnea, and site-specific pain) and treatment-related symptoms (sore mouth, dysphagia, peripheral neuropathy, and alopecia) [Bergman, B., et al 1994]. It is scored on a 4-point scale (1 = not at all, 2 = a little, 3 = quite a bit, and 4 = very much) and has been translated and validated into more than 60 languages.

The EORTC QLQ-C30 and QLQ-LC13 are the most frequently used and reported PRO measures in lung cancer clinical studies. The reliability, validity, and practicality of these instruments have been reported [Aaronson, N. K., et al 1993a] [Bergman, B., et al 1994].

4.2.1.3.3 EuroQoL EQ-5D

The EuroQoL-5D (EQ-5D) 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]Rabin, 2001. The 5 health state dimensions in the EQ-5D include the following: mobility, selfcare, 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 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].

4.2.1.4 Pharmacokinetic Endpoints

Standard PK parameters of clearance and volume of distribution at steady state are planned to be calculated for lenvatinib when co-administered with pembrolizumab in this study using the accepted mixed effects modeling approach. PK data obtained from this study may be combined with data from other studies and analyzed using standard population PK techniques to further characterize basic PK parameters, explore the exposure-response relationship for lenvatinib antitumor activity, evaluate the effect of extrinsic and intrinsic factors in support of the proposed dosing regimen, and evaluate safety in the proposed patient population.

4.2.1.5 Planned Exploratory Biomarker Research

Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies, including novel combinations with antiangiogenesis therapy, is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy and other treatments administered, as well as determinants of AEs in the course of our clinical studies. These efforts may identify novel predictive/PD biomarkers and generate information that may better guide single-agent and combination therapy with immuno-oncology drugs. To identify novel biomarkers, biospecimens (ie, blood components, tumor material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include but are not limited to:

Germline (blood) genetic analyses (eg, SNP analyses, whole exome sequencing, whole genome sequencing)

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations.

Genetic (DNA) analyses from tumor

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, microsatellite instability), contributing towards the development/progression of cancer and/or driving response to therapy. Key molecular changes of interest to immuno-oncology drug development include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a ‘hyper-mutated’ state) may generate neo-antigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Evaluation of molecular targets and signaling pathways including angiogenesis and growth factor related signaling pathways related to

lenvatinib and pembrolizumab may also be explored. Thus, genome-wide approaches may be used for this effort. Note that in order to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Circulating tumor DNA and/or RNA may also be evaluated from blood samples.

Tumor and blood RNA analyses

Both genome-wide and targeted messenger RNA (mRNA) expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that correlate to clinical response to treatment with pembrolizumab or other immunotherapies. Pembrolizumab induces a response in tumors that likely reflects an inflamed/immune phenotype. Specific immune-related gene sets (ie, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system and growth factor signaling pathways (eg, VEGF and FGF) may also be evaluated. MicroRNA profiling may also be pursued as well as exosomal profiling.

Proteomics and immunohistochemistry (IHC) using blood or tumor

Tumor and blood samples from this study may undergo proteomic analyses (eg, PD-L1 IHC). PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in patients with NSCLC, and an in vitro diagnostic (IVD) device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicates that this association may also be true in additional cancer types (ie, triple negative breast, head and neck, and gastric). Additional tumor or blood-derived proteins may also correlate with response to pembrolizumab and lenvatinib combination therapy. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include but are not limited to immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab (MK-3475) and lenvatinib combination therapy.

Other blood-derived biomarkers

In addition to expression on the tumor tissue, PD-L1, circulating cytokines and angiogenic factors, and other tumor-derived proteins can be shed from tumor and released into the blood. Assays such as enzyme-linked immunoassay (ELISA) measure such proteins in serum. Correlation of expression with response to pembrolizumab and lenvatinib combination therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

Other molecular changes of interest include the subtype of T-cells in the tumor microenvironment. The T-cell repertoire from tumor tissue and blood components may be evaluated.

4.2.2 Rationale for the Use of Comparator/Placebo

No comparator/placebo will be used in Part 1 (safety run-in). In Part 2, participants will be randomized to receive lenvatinib or matching placebo. Both treatment arms will receive platinum doublet chemotherapy and pembrolizumab.

Based on the results of KEYNOTE-021G and KEYNOTE-189, standard 1L therapy for nonsquamous NSCLC, without activating mutations such as *EGFR* mutations or *ALK* fusion, is chemotherapy in combination with pembrolizumab, which has shown a 1-year OS of 70% compared to 50% with chemotherapy alone. For patients with high PD-L1 expression, pembrolizumab is given as monotherapy, with an expected 2-year OS of 52% [Brahmer, J. R., et al 2017]. The results from KEYNOTE studies establish pembrolizumab plus chemotherapy as an efficacious option for 1L treatment in patients with NSCLC and a valid comparator that new treatment combinations will need to surpass. The use of lenvatinib/matching placebo in combination with pembrolizumab and chemotherapy will ensure the objectivity of the local investigators' treatment decisions and AE causality assessments, while still providing participants SOC treatment.

4.3 Justification for Dose

4.3.1 Maximum Dose/Exposure for This Study

NOTE: In alignment with the study-specific investigator letter dated 20-SEP-2023, all study participants still receiving study treatment should continue to receive therapy on study and undergo modified protocol study procedures as specified in this amendment. Participants currently on study treatment with lenvatinib can continue treatment per investigator's discretion. Participants who are potential candidates for Second Course treatment will continue in Efficacy Follow up.

In this study, the maximum doses for lenvatinib and pemetrexed are 8 mg qd and 500 mg/m^2 Q3W, respectively. There is no maximum number of administrations for either lenvatinib or pemetrexed. The maximum dose and exposure for pembrolizumab in this study is 200 mg Q3W for up to 35 administrations (~ 2 years); however, participants may be eligible for an additional 17 administrations (~ 1 year; See Section 7.1.1). The maximum dose/exposure for carboplatin and cisplatin is 4 administrations (AUC 5 mg/mL/min for carboplatin, 75 mg/m^2 for cisplatin both given Q3W).

4.3.2 Lenvatinib Dosing

The dosing regimen of lenvatinib was selected based on the results of a Phase 1 dose-finding study (Study E7080-J081-110) conducted in Japan with chemotherapy-naïve NSCLC, in which lenvatinib was tested in combination with carboplatin (AUC 6 mg/mL/min) and paclitaxel 200 mg/m^2 to establish an MTD. The MTD of lenvatinib was determined to be 4 mg BID after DLTs were experienced at 6 mg BID (febrile neutropenia/gingival infection [n=2]). A dose-expansion cohort was added, and 28 participants were dosed in total: 12 in the dose-finding cohort and 16 participants in the dose-expansion cohort. In total, 22 participants were dosed at 4 mg BID with 6 dosed at 6 mg BID. The most frequent Grade 3 and Grade 4

toxicities were neutropenia (95%), leukopenia (50%), hypertension (36%), thrombocytopenia (27%), and febrile neutropenia (23%) [Nishio, M., et al 2013]. The rate of hematologic toxicities was not deemed to be significantly different from this chemotherapy regimen alone [Ohe, Y., et al 2007].

In a small Phase 2 study (HOT 0902) by the Hokkaido Lung Cancer Clinical Study Group, carboplatin (AUC 5 mg/mL/min) and pemetrexed (500 mg/m^2) were examined for efficacy and toxicity. Only 29.3% and 2.4% of patients developed Grade 3 or Grade 4 neutropenia and febrile neutropenia, respectively. Grade 3 and Grade 4 thrombocytopenia was seen in 17% of patients [Kanazawa, K., et al 2014]. These data suggest that some hematologic toxicities seen with the combination of lenvatinib plus carboplatin and paclitaxel in Study E7080-J081-110 can be mitigated by the use of carboplatin and pemetrexed.

Modeling of PK data from Phase 1 lenvatinib studies examining BID versus qd dosing demonstrated that higher drug exposure from qd dosing correlated with improved PFS or tumor response compared to BID dosing. Since there were no differences between the 2 dosing regimens in term of safety or tolerability, qd dosing was recommended for ongoing and future studies of lenvatinib [Gupta, A., et al 2010]. As such, lenvatinib dosing for this study will be 8 mg qd.

4.3.3 Pembrolizumab Dosing

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (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 OS at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment-naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q3W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other

tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

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

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

4.3.4 Chemotherapy Dosing

The dosing regimens of chemotherapy represent the SOC per the approved product labels. Chemotherapy may be reduced, interrupted, or discontinued as outlined in Table 8 and Table 9, at the investigator's discretion, or according to applicable local label recommendations, if more stringent.

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 consen, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

Upon study termination, participants are discontinued and may be enrolled in a pembrolizumab extension study, if available.

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

Male/female participants with metastatic NSCLC, who have not received systemic anticancer therapy for their metastatic disease and are at least 18 years of age may 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

A participant will be eligible for inclusion in the study if the participant:

1. Have a histologically or cytologically confirmed diagnosis of Stage IV (American Joint Committee on Cancer [AJCC], version 8 or current version) nonsquamous NSCLC.

   Note: Mixed tumors will be categorized by the predominant cell type; if small cell elements are present, the participant is ineligible.

2. Have confirmation that *EGFR*-, *ALK*-, or *ROS1*-directed therapy is not indicated as primary treatment (documentation of absence of tumor-activating *EGFR* mutations AND absence of *ALK* and *ROS1* gene rearrangements OR presence of a *KRAS* mutation).

3. Have measurable disease per RECIST 1.1.

   Note: Lesions that appear measurable, but are situated in a previously irradiated area, can be considered measurable (eligible for selection as target lesions) if they have shown documented growth since the completion of irradiation.

4. Have provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue. Formalin fixed specimens after the participant has been diagnosed with metastatic disease are preferred. Biopsies obtained prior to receipt of adjuvant/neoadjuvant chemotherapy are permitted if recent biopsy is not feasible.

Demographics

5. Be male or female ≥18 years of age inclusive, at the time of signing the informed consent form (ICF).

6. Have a life expectancy of at least 3 months.

7. Have an ECOG performance status of 0 or 1 within 7 days prior to the first dose of study intervention but before randomization.

Male Participants

Contraceptive use by men 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.

8. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 7 days after the last dose of lenvatinib/matching placebo and up to 180 days after the last dose of chemotherapeutic agents:

   • Refrain from donating sperm

   PLUS either:

   • Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

   OR

   • Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below:

     - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

       Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

   Note: 7 days after lenvatinib/matching placebo is stopped, if the participant is on pembrolizumab only and is greater than 180 days post chemotherapy, no male contraception measures are needed.

Female Participants

Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

9. 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 and 30 days post-lenvatinib/matching placebo, and up to 180 days post last dose of chemotherapeutic agents, whichever occurs last. 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 located 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.

Informed Consent

10. The participant (or legally acceptable representative) has provided documented informed consent for the study.

Laboratory Values

11. Have adequate organ function as defined in the following table (Table 2). Specimens must be collected and reviewed within 10 days prior to the start of study intervention.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematologic	
Absolute neutrophil count (ANC)	≥1500/µL
Platelet count	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[1]
Renal	
Serum Creatinine OR Measured or calculated CrCl[2] (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥60 mL/min for participant with creatinine levels >1.5 × the institutional ULN
Hepatic	
Total bilirubin OR Direct bilirubin	Total bilirubin ≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
INR or PT Activated partial thromboplastin time (aPTT)[3]	≤1.5 × ULN unless the participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

Abbreviations: aPTT = activated partial thromboplastin time; ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCl = creatinine clearance; GFR=glomerular filtration rate; INR = international normalized ratio; PT = prothrombin time; ULN=upper limit of normal.

[1] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[2] CrCl should be calculated per institutional standard.

[3] PTT may be performed if the local laboratory is unable to perform aPTT.

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

12. Have adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP ≤150/90 mm Hg and no change in antihypertensive medications within 1 week prior to randomization.

5.2 Exclusion Criteria

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

Medical Conditions

1. Has known untreated central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable (ie, without evidence of progression for at least 4 weeks by repeat imaging [the repeat imaging must be performed during the screening period]), clinically stable, and have not required steroids for at least 14 days prior to the first dose of study intervention.

2. Has a history of (noninfectious) pneumonitis that required systemic steroids or current pneumonitis/interstitial lung disease.

3. Radiographic evidence of intratumoral caviations, encasement, or invasion of a major blood vessel. Additionally, the degree of proximity to major blood vessels should be considered for exclusion because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis after lenvatinib therapy. (In the chest, major blood vessels include the main pulmonary artery, the left and right pulmonary arteries, the 4 major pulmonary veins, the superior or inferior vena cava, and the aorta).

4. Has a known history of an additional malignancy, except if the participant has undergone potentially curative therapy with no evidence of that disease recurrence for at least 3 years since initiation of that therapy.

    - Note: The time requirement for no evidence of disease for at least 3 years does not apply to the NSCLC for which a participant is enrolled in the study. The time requirement also does not apply to participants who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, in situ cervical cancer, or other in situ cancers.

5. Has an active autoimmune disease 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, etc.) is allowed.

6. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (doses exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study intervention.

7. Has had an allogeneic tissue/solid organ transplant.

8. Has a known history of human immunodeficiency virus (HIV) infection. HIV testing is not required unless mandated by the local health authority.

9. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive or HBV-DNA detected) or known active Hepatitis C virus (defined as HCV RNA [qualitative] detected or HCV antibody reactive, if HCV-RNA is not the local SOC) infection. No testing for Hepatitis B or Hepatitis C is required unless mandated by the local health authority.

10. Has a history of a gastrointestinal condition or procedure that in the opinion of the investigator may affect oral drug absorption.

11. Has active hemoptysis (at least 0.5 tsp of bright red blood) within 2 weeks prior to the first dose of study intervention.

12. Has significant cardiovascular impairment within 12 months prior to the first dose of study intervention, including history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction, cerebrovascular accident (CVA)/stroke, or cardiac arrhythmia associated with hemodynamic instability.

13. Has a known history of active tuberculosis.

14. Has an active infection requiring systemic therapy.

15. 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.

16. Has known psychiatric or substance abuse disorders that would interfere with the participant's cooperation to meet with the requirements of the study.

17. Previously had a severe hypersensitivity reaction to treatment with a monoclonal antibody or has a known sensitivity to any component of lenvatinib or pembrolizumab, or as applicable, carboplatin, cisplatin, or pemetrexed.

18. A WOCBP who has a positive urine pregnancy test within 24 hours prior to randomization or treatment allocation (see Appendix 5). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

    Note: In the event that 24 hours have elapsed between the Screening pregnancy test and the first dose of study intervention, another pregnancy test (urine or serum) must be performed and must be negative in order for the participant to start receiving study medication.

19. Has preexisting ≥Grade 3 gastrointestinal or non-gastrointestinal fistula.

Prior/Concomitant Therapy

20. Has received prior systemic chemotherapy or other targeted or biological antineoplastic therapy for their metastatic NSCLC.

    Note: Prior treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic NSCLC.

21. Has received prior treatment with pembrolizumab or any other anti-PD-1, anti-PD-L1, anti-PD-L2 agent, with lenvatinib or any other RTKi, or with an agent directed to another stimulatory or co-inhibitory T cell receptor (eg, CTLA-4, OX-40, CD137, GITR).

22. Has received radiotherapy within 14 days prior to the first dose of study intervention or received lung radiation therapy of >30 Gy within 6 months prior to the first dose of study intervention.

    Note: Participants must have recovered from all radiation-related toxicities to Grade ≤1, not required corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

23. Has received systemic steroid therapy (in doses exceeding 10 mg daily of prednisone equivalent) within 7 days prior to the first dose of study intervention.

24. Has received a live or live attenuated vaccine within 30 days prior to the first dose of study intervention. Note: killed vaccines are allowed.

Prior/Concurrent Clinical Study Experience

25. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks prior to the first dose of study intervention.

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

Diagnostic Assessments

26. Participants with proteinuria >1+ on urine dipstick testing/urinalysis will undergo 24-hour urine collection for quantitative assessment of proteinuria. Participants with urine protein ≥1 g/24 hours will be ineligible.

27. Has a prolongation of QTc interval (calculated using Fridericia's formula) of >480 msec

28. Has left ventricular ejection fraction (LVEF) below the institutional (or local laboratory) normal range as determined by multigated acquisition scan (MUGA) or echocardiogram (ECHO).

Other Exclusions

29. 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 ability to participate for the full duration of the study, or make it not in the best interest of the participant to participate, in the opinion of the treating investigator.

Note: Country-specific requirements are listed in Appendix 7.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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

5.3.2 Contraception

Lenvatinib and pembrolizumab may have adverse effects on a fetus in utero. Refer to Appendix 5 for approved methods of 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 study intervention may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, participants of childbearing potential must adhere to the contraception requirements (Appendix 5) from the first day of study intervention initiation (or 14 days prior for oral contraception) throughout the treatment period and up to 120 days post pembrolizumab and/or 30 days post-lenvatinib/matching placebo and up to 180 days after last dose of chemotherapeutic agents. 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 treatment with lenvatinib or pembrolizumab, 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 an SAE (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. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described above.

5.3.4 Use in Nursing Women

It is unknown whether lenvatinib or pembrolizumab 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 consent 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.

Clinical supplies will be packaged to support enrollment and 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 3.

NOTE: In alignment with the study-specific investigator letter dated 20-SEP-2023, all study participants still receiving study treatment should continue to receive therapy on study and undergo modified protocol study procedures as specified in this amendment. Participants currently on study treatment with lenvatinib can continue treatment per investigator's discretion. Participants who are potential candidates for Second Course treatment will continue in Efficacy Follow up.

Table 3 Study Treatments

Arm Name	Arm Type	Study Treatment Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin-istration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
Part 1 and Part 2: Arm 1	Experimental	Lenvatinib	Drug	Capsule	4 mg and 1 mg	8 mg	Oral	Once daily; no treatment duration limit	Experimental	IMP	Central
Part 2: Arm 2	Placebo comparator	Matching placebo	Drug	Capsule	N/A	N/A	Oral	Once daily; no treatment duration limit	Placebo	IMP	Central
Part 1 and Part 2: Arms 1 and 2	Experimental/ Placebo comparator	Pembro-lizumab (MK-3475)	Drug	Solution for infusion	25 mg/mL	200 mg	IV infusion	Once every 3 weeks; up to a total of 35 cycles	Standard of care/ Experimental	IMP	Central
Part 1 and Part 2: Arms 1 and 2[1]	Experimental/ Placebo comparator	Carboplatin	Drug	Solution for infusion	10 mg/mL	AUC 5 mg/mL/min	IV infusion	Once every 3 weeks; up to the first 4 cycles of treatment	Standard of care	NIMP	Local or Central
Part 1 and Part 2: Arms 1 and 2[1]	Experimental/ Placebo comparator	Cisplatin	Drug	Solution for infusion	1 mg/mL	75 mg/m^2	IV infusion	Once every 3 weeks; up to the first 4 cycles of treatment	Standard of care	NIMP	Local or Central
Part 1 and Part 2: Arms 1 and 2[1]	Experimental/ Placebo comparator	Cisplatin	Drug	Lyophilized Powder	20 mg	75 mg/m^2	IV infusion	Once every 3 weeks; up to the first 4 cycles of treatment	Standard of care	NIMP	Local or Central

Arm Name	Arm Type	Study Treatment Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin-istration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
Part 1 and Part 2: Arms 1 and 2[1]	Experimental/ Placebo comparator	Pemetrexed	Drug	Lyophilized powder	500 mg/ vial	500 mg/m^2	IV infusion	Once every 3 weeks; no treatment duration limit	Standard of care	NIMP	Local or Central

Abbreviations: AUC = area under the plasma drug concentration-time curve; IMP = Investigational Medicinal Product; IV = intravenous; NIMP = Non-Investigational Medicinal Product

Definitions of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) are based on guidance issued by the European Commission. Regional and/or country differences in the definitions may exist. In these circumstances, local legislation is followed.

[1] Clinical supply concentration and formulation of chemotherapy may vary by local sourcing.

All supplies indicated in Table 3 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.

The investigator will select one of the following platinum doublet chemotherapy regimens prior to randomization:

- Pemetrexed 500 mg/m^2 + carboplatin AUC 5 mg/mL/min Q3W for 4 cycles followed by maintenance therapy with pemetrexed 500 mg/m^2 Q3W until reaching a discontinuation criterion listed in Section 7.1

- Pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 for 4 cycles followed by maintenance therapy with pemetrexed 500 mg/m^2 Q3W until reaching a discontinuation criterion listed in Section 7.1

All participants will also receive pembrolizumab 200 mg Q3W for up to a total of 35 cycles and lenvatinib (Part 1 and Part 2: Arm 1)/matching placebo (Part 2: Arm 2) until reaching a discontinuation criterion listed in Section 7.1. There is no treatment duration limit for lenvatinib/matching placebo or pemetrexed.

Part 1 will be an unblinded, open-label, safety run-in. In Part 2, treatment with lenvatinib/matching placebo will be double-blinded. Matching placebo was created by the Sponsor to match the active product.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Chemotherapy should be prepared per the approved product labels. Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual. Participants/caregivers will be given instructions on how to handle and store lenvatinib capsules at home.

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

Intervention allocation/randomization will occur centrally using an IVRS/IWRS. Participants in Part 1 (safety run-in) will receive lenvatinib in combination with pembrolizumab and platinum doublet chemotherapy without randomization. In Part 2 (Phase 3 study), participants will be assigned randomly in a 1:1 ratio to lenvatinib in combination with platinum doublet chemotherapy plus pembrolizumab (Arm 1) or matching placebo in combination with platinum doublet chemotherapy plus pembrolizumab (Arm 2).

6.3.2 Stratification

Part 1 (safety run-in):

There are no stratification factors for Part 1.

Part 2 (Phase 3 Study):

Treatment assignment in Part 2 will be stratified by the following factors:

1. PD-L1 TPS (<50% vs. ≥50%)
2. Geographic site (East Asian vs. non-East Asian)
3. ECOG performance status at Screening (0 vs. 1)

6.3.3 Blinding

As of the final analysis, the study was unblinded. Original protocol text that is contained in this section has been retained for reference.

Part 1 (safety run-in):

Part 1 of this study is being conducted as an open-label study, ie, participants, investigators, and Sponsor personnel will be aware of study intervention assignments.

Part 2 (Phase 3 Study):

In Part 2, a double-blinding technique with in-house blinding will be used. Lenvatinib/matching placebo will be packaged identically for Arms 1 and 2 so that the blind is maintained. The participant, the investigator, the Sponsor, and delegate(s) who are involved in study intervention administration or the clinical evaluation of participants will be unaware of treatment assignments.

The treatment identity of pembrolizumab and chemotherapy will be open-label; the identity of those treatments will be known by the participant, the investigator, the Sponsor, and delegate(s) who are involved in study intervention administration or the clinical evaluation of participants.

See Section 8.1.10 for a description of the method of unblinding a participant during the study, should such action be warranted.

The central vendor PD-L1 TPS results of participants will be blinded to the investigator. The Sponsor acknowledges that due to the commercial availability of PD-L1 testing assays, it is possible that the investigator may know a participant's TPS prior to Screening. This risk is seen as acceptable, as the treatment interventions are hypothesized to provide benefit regardless of TPS.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment for >28 days (lenvatinib), >6 weeks (chemotherapy), or >12 weeks (pembrolizumab) require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the treatment period. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study intervention may be required. The investigator is to discuss prohibited medication/vaccination 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 but the decision to continue the

participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

All prior medications (including over-the-counter medications) administered within 30 days prior to 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 (or 90 days if used to treat an SAE) 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 interventions may be continued during the study.

6.5.1 Allowed Concomitant Medications

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 interventions. Antiemetic drugs or any other prophylaxis treatment should be considered in accordance with institutional guidelines.

The following concomitant medications are also allowed:

- Hormone replacement therapy
- Thyroid hormone suppressive therapy
- Anticoagulants including low molecular-weight heparin (LMWH), warfarin, anti-Xa agents
- Anti-inflammatory agents
- Bisphosphonates or denosumab
- Antihypertensive therapy (including additional antihypertensive treatment as appropriate if BP increases once the participant is enrolled)
- Colony-stimulating factors

  Use of colony-stimulating factors (CSFs) for primary prophylaxis is permitted at the investigator's discretion. Refer to the American Society of Clinical Oncology guidelines for use of CSFs [Smith, T. J., et al 2006].

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 periods of this study:

- Concurrent anticancer therapies such as chemotherapy, targeted therapies, antitumor interventions (surgical resection, surgical debulking of tumor, etc.), or cancer immunotherapy not specified in this protocol

  Note: Topical anticancer agents to treat skin lesions (eg, in situ melanoma or squamous cell carcinoma) are allowed, excluding skin metastasis of melanoma.

- Other concurrent investigational drugs

- Live or live attenuated vaccines within 30 days prior to the first dose of study intervention and while participating in the study.

  Note: killed vaccines are allowed.

- Systemic glucocorticoids for any purpose other than listed in Section 6.5.4.1.

- Radiation therapy for disease control.

  Note: Palliative radiotherapy is permitted for nontarget lesions if considered medically necessary by the treating physician and upon discussion with the Sponsor.

- Phenytoin during treatment with carboplatin/cisplatin

For participants who, at the discretion of the investigator, require the use of any of the aforementioned treatments for clinical management, continuation of the study interventions and further participation in the study must be discussed and agreed upon with the Sponsor.

If participants receive additional anticancer therapies, this will be judged to represent evidence of disease progression, and study interventions will be discontinued. These participants should complete all end of treatment assessments and continue to be followed for survival as outlined in the SoA.

Country-specific requirements are listed in Appendix 7.

6.5.3 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 DDI 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 coadministration of lenvatinib with either inducers or inhibitors of CYP3A4/P-glycoprotein (P gp) 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 non-enzymatic processes (lenvatinib IB).

6.5.4 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6.2.

Note: If after evaluation of an event, it is determined not to be related to pembrolizumab or lenvatinib, the investigator does not need to follow the treatment guidance.

6.5.4.1 Systemic Corticosteroid Use

Systemic corticosteroids are permitted in the following situations:

- To mediate potential immune-related AEs as guided in Table 5.
- As premedication/post medication to prevent AEs associated with chemotherapy or IV contrast.
- Brief, limited use of systemic corticosteroids (≤7 days) is permitted where such use is considered SOC (eg, for chronic obstructive pulmonary disease exacerbation).
- Replacement doses of steroids (ie, ≤10 mg daily of prednisone equivalent) and the use of local steroid injections and topical steroids are permitted while on study.

6.5.4.2 Antiemetic Use

For participants receiving chemotherapy, antiemetic therapy should follow Multinational Association of Supportive Care in Cancer ([MASCC]; Appendix 9) or appropriate local guidelines and should, for the first 4 cycles, include a 5-HT3 receptor antagonist, dexamethasone (or equivalent), and aprepitant (or equivalent NK-1 receptor antagonist) as per the guideline followed.

6.5.4.3 Colony-stimulating Factors

For participants receiving chemotherapy, the American Society of Clinical Oncology (ASCO) guidelines for use of CSFs, or local equivalent, should be used for patient

management [Smith, T. J., et al 2006]. Use of CSFs for primary prophylaxis is permitted at the investigator's discretion.

6.5.4.4 Cisplatin Premedication

Hydration is necessary to cause sufficient diuresis during and after treatment with cisplatin. All participants should receive adequate hydration from 2 to 12 hours before administration until a minimum of 6 hours after administration of cisplatin per the local label.

6.5.4.5 Pemetrexed Premedication

All participants must receive the appropriate supplementation of vitamin B12, folic acid, and corticosteroid prophylaxis as listed below or per the local label:

- Folic acid, 350 µg to 1000 µg orally: At least 5 doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, through the full course of therapy, and for 21 days after the last dose of pemetrexed.

- Vitamin B12, 1000 µg by intramuscular (IM) injection: vitamin B12 must be given in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent vitamin B12 injections may be given on the same day as pemetrexed.

- Dexamethasone prophylaxis, 4 mg orally twice per day (or equivalent): Dexamethasone may be taken the day before, day of, and day after pemetrexed administration. Higher or additional doses are permitted for antiemetic prophylaxis during Cycles 1 through 4 but are not to exceed doses in MASCC guidelines (or local equivalent) (Appendix 9).

6.6 Dose Modification (Escalation/Titration/Other)

NOTE: In alignment with the study-specific investigator letter dated 20-SEP-2023, all study participants still receiving study treatment should continue to receive therapy on study and undergo modified protocol study procedures as specified in this amendment. Participants currently on study treatment with lenvatinib can continue treatment per investigator's discretion. Participants who are potential candidates for Second Course treatment will continue in Efficacy Follow up.

6.6.1 Lenvatinib

Lenvatinib dose reduction and interruption for participants who experience lenvatinib/pembrolizumab combination therapy-related toxicity will be in accordance with the dose modification guidelines described in Table 4. 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 is required.

The starting dose of lenvatinib is 8 mg/day. Dose reductions of lenvatinib occur in succession based on the previous dose level as outlined in Table 4. Any dose reduction below 2 mg/day must be discussed with the Sponsor. Once the dose of lenvatinib/matching placebo 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), posterior reversible encephalopathy syndrome (PRES)/reversible posterior leukoencephalopathy syndrome ([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 4). For overlapping toxicities of pembrolizumab and lenvatinib/matching placebo, please refer to Section 6.6.4.

Table 4 Dose Modification Guidelines for Lenvatinib-related Adverse Events

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 6 mg/day
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 4 mg/day
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 2 mg/day
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 grades).

a. An interruption of lenvatinib/placebo 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 treatment 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 study intervention should be discussed with the 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/matching placebo. See Sections 6.6.1.2 and 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 a 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 medication for at least 1 week prior to 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 the 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 (ie, 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 participants already on antihypertensive medication, treatment modification may be necessary if hypertension persists.

Lenvatinib/matching placebo 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 co-morbidities). Once the participant has been on the same antihypertensive medications for at least 48 hours and the BP is controlled, lenvatinib/matching placebo should be resumed as described below.

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

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

1. Continue study 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 treatment can be continued without dose modification.

3. If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted and restarted at a lower dose 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/matching placebo administration should be interrupted and restarted at an additional dose reduction only when systolic BP is ≤150 mm Hg and diastolic BP is ≤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/matching placebo administration should be interrupted and restarted at a third dose reduction only when systolic BP is ≤150 mm Hg and diastolic BP is ≤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 lenvatinib/matching placebo.

6.6.1.2 Management of Proteinuria

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

Detection and Confirmation

1. Perform urine dipstick testing per the SoA (Section 1.3).

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 proteinuria ≥2+ on urine dipstick/urinalysis while on lenvatinib/matching placebo

- A subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib/matching placebo dose level

- When there has been a lenvatinib/matching placebo dose reduction, and at the new dose level, the urine protein dipstick result is ≥2+

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

Grading of Proteinuria

- Grading according to the NCI CTCAE, v4.0 will be based on the 24-hour urinary protein result if one has been obtained. Management of lenvatinib administration will be based on the grade of proteinuria according to Table 4.

Monitoring

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

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

- In the event of nephrotic syndrome, lenvatinib/placebo must be discontinued.

6.6.1.3 Management of Diarrhea

An anti-diarrheal 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 anti-diarrheal agent should be individualized to the participant's clinical circumstances and follow standard medical practice. If signs/symptoms of diarrhea persist despite optimal medical management, instructions contained in Table 4, Table 5, and/or Table 9 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) and as clinically indicated. If signs/symptoms indicating liver injury occur, instructions contained in Table 4, Table 5, and/or Table 9 should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs, study intervention must be discontinued.

6.6.1.5 Management of Thromboembolic Events

Participants should be advised to pay attention to symptoms suggestive of venous thromboembolic events which include acute onset of shortness of breath, dyspnea, chest pain,

cough, hemoptysis, tachypnea, tachycardia, cyanosis, DVT signs including lower extremity swelling, and warmth to touch or tenderness. In case any of these symptoms appear, participants should be instructed to report their symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in Table 4 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/placebo 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 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 4 should be followed.

6.6.1.7 Management of Hypocalcemia

Serum calcium should be monitored per the SoA (Section 1.3). 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 cases, total (uncorrected) serum calcium should be used.

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 4 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 patients at higher risk. For patients requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ. Withhold lenvatinib if ONJ develops and restart based on clinical judgment of adequate resolution (See Section 6.6.4).

6.6.1.12 Other Allowed Dose Interruptions for Lenvatinib

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.

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

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

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

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 5.

For overlapping toxicities of pembrolizumab and lenvatinib/matching placebo, please refer to Section 6.6.4.

Table 5 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 6. Management guidelines for toxicities deemed related to both pembrolizumab and lenvatinib are outlined in Section 6.6.4.

Table 6 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

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

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
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 Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

6.6.2.3 Other Allowed Dose Interruption(s) for Pembrolizumab

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

Interruptions from the protocol-specified treatment plan for more than 12 weeks between pembrolizumab doses for nondrug-related or administrative reasons require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.6.3 Chemotherapy

Recommended dose modifications for key chemotherapy toxicities are outlined in Table 7, Table 8, and Table 9. These serve only as a guide and do not replace investigator judgment and applicable local label recommendations, if more stringent.

Table 7 Chemotherapy Dose Level Definitions

	Dose Level 0	**Dose Level -1**	**Dose Level -2**	**Dose Level -3**
Carboplatin	AUC 5 mg/mL/min Maximum dose 750 mg	AUC 3.75 mg/mL/min Maximum dose 562.5 mg	AUC 2.5 mg/mL/min Maximum dose 375 mg	Discontinue treatment
Cisplatin	75 mg/m^2	56 mg/m^2	38 mg/m^2	Discontinue treatment
Pemetrexed	500 mg/m^2	375 mg/m^2	250 mg/m^2	Discontinue treatment
Abbreviation: AUC = area under the plasma drug concentration-time curve				

Table 8 Recommended Dose Modifications for Chemotherapy-related Hematological Toxicities

Platelets		ANC	Carboplatin/Cisplatin	Pemetrexed
			Dose level from Table 7	
≥50,000/mcL	AND	≥500/mcL	DL 0	DL 0
≥50,000/mcL	AND	<500/mcL	DL -1	DL -1
<50,000/mcL without bleeding	AND	ANY	DL -1	DL -1
<50,000/mcL with Grade ≥2 bleeding	AND	ANY	DL -2	DL -2
ANY	AND	<1,000/mcL + fever ≥38.5°C (101°F)	DL -1	DL -1
Abbreviation: ANC = absolute neutrophil count; DL = dose level				

Table 9 Recommended Dose Modifications for Chemotherapy-related Nonhematological Toxicities

Event	CTCAE Grade	Carboplatin	Cisplatin	Pemetrexed
		Dose level from Table 7		
Nausea or vomiting	Grade 3 or 4	DL 0	DL 0	DL 0
Diarrhea	Grade 3 or 4	DL 0	DL -1	DL -1
Mucositis	Grade 3 or 4	DL 0	DL 0	DL -2
Neurotoxicity	Grade 2	DL 0	DL -2	DL 0
	Grade 3 or 4	DL -1	Discontinue treatment	DL -1
Transaminase elevation	Grade 3	DL -1	DL -1	DL -1
	Grade 4	Discontinue treatment	Discontinue treatment	Discontinue treatment
Other nonhematological toxicities	Grade 3 or 4	DL -1	DL -1	DL -1
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; DL = dose level				

Creatinine clearance (CrCl): CrCl will be based on the original weight-based Cockcroft and Gault formula or institutional standard. CrCl must be ≥45 mL/min prior to the administration of chemotherapy. Platinum chemotherapy and/or pemetrexed may be delayed for up to 42 days to allow the participant time to recover from the toxicity. If a participant's CrCl value has not returned to ≥45 mL/min within 42 days after the previous dose, platinum chemotherapy and/or pemetrexed must be discontinued.

6.6.4 Dose Modifications for Overlapping Toxicities

Based on the known toxicity profiles of pembrolizumab and lenvatinib, certain treatment-related AEs are uniquely associated with one drug versus the other. For example, hypertension, arterial thrombotic events, proteinuria, and hemorrhagic events are known risks for lenvatinib treatment, while immune-related AEs are risks for pembrolizumab treatment. However, certain AEs, such as such as diarrhea, hypothyroidism, and liver enzyme elevation, may be initially considered attributable to either study drug. Therefore, evaluation of attribution is important for determining the study 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.

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

   a) ALT or AST >5 X ULN for more than 2 weeks.

   Pembrolizumab will have already been permanently discontinued per [Table 5], but lenvatinib may be administered at a reduced dose by the time this criterion is met and must be permanently discontinued immediately.

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

Although [Table 5] advises pembrolizumab to be withheld (interrupted), and [Table 4] advises lenvatinib to have no dose modification or a reduction, if this criterion is met, both drugs must be permanently discontinued immediately.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

Treatment with pembrolizumab and chemotherapy in this study is open-label; therefore, the participant, the investigator, the Sponsor, and delegate(s) who are involved in study intervention administration or the clinical evaluation of participants are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

The emergency unblinding call center will use the treatment/randomization schedule for the study to unblind participants and to unmask study intervention identity of lenvatinib or matching placebo. In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic treatment allocation/randomization system (IVRS/IWRS) should be used in order to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 8.1.10, Participant Blinding/Unblinding, for a description of the method of unblinding a participant during the study, should such action be warranted.

6.9 Standard Policies

At the close of the study after treatment unblinding, a letter is to be sent by the investigator to those participants who received placebo in the image of the competitor's product to provide the following information:

"You have participated in a study conducted by MSD. This is to advise you that you were among those who received a look-alike tablet created by the Sponsor to resemble the drug lenvatinib as much as possible. You did not receive the active drug lenvatinib manufactured by Eisai Co., Ltd."

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 8.12.3.

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 interrupts study intervention administration of lenvatinib for more than 28 days, except if agreed to by the Sponsor.

- The participant interrupts study intervention administration of pembrolizumab for more than 12 weeks, except if agreed to by the Sponsor.

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

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

Pembrolizumab will have already been permanently discontinued per [Table 5], but lenvatinib may be administered at a reduced dose by the time this criterion is met and must be permanently discontinued immediately.

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

Although [Table 5] advises pembrolizumab to be withheld (interrupted), and [Table 4] advises lenvatinib to have no dose modification or a reduction, if this criterion is met, both drugs must be permanently discontinued immediately.

- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or the Sponsor, places the participant at unnecessary risk from continued administration of study intervention.

- The participant has a confirmed positive serum pregnancy test.

- Disease progression is radiographically documented and verified by BICR per RECIST 1.1 (after obtaining informed consent addendum and Sponsor communication, the investigator may elect to continue treatment beyond confirmed PD per iRECIST).

- Intercurrent illness that prevents further administration of treatment.

- The participant has any progression or recurrence of any malignancy, or occurrence of another malignancy that requires active treatment. Exceptions to secondary malignancies include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, new nonulcerated primary melanoma <1 mm in depth with no nodal involvement, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy. Exceptions should be discussed with the Sponsor before continuing treatment or remaining in follow-up.

- Unacceptable toxicity.

- Investigator's decision to discontinue treatment.

- Administrative reasons requiring cessation of treatment.

- For carboplatin, cisplatin, and pembrolizumab ONLY: Treatment completion (4 cycles of carboplatin or cisplatin/35 cycles of pembrolizumab).

  Note: The number of treatments is calculated starting with the first dose. Participants who stop the combination or pembrolizumab after receiving 35 doses may be eligible for retreatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.1. Participants may be retreated in the Second Course Phase (Retreatment) for up to an additional 17 cycles (approximately 1 year).

- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6.

7.1.1 Second Course Treatment

Participants are allowed to start Second Course Treatment with investigator assessed PD. Original protocol text that is contained in this section has been retained for reference.

All participants who stop study intervention with SD or better may be eligible for up to an additional 17 cycles (approximately 1 year) of pembrolizumab treatment if they progress after stopping study intervention from the initial treatment phase. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the participant meets the following conditions:

Either

- Stopped initial study intervention after attaining an investigator-determined confirmed CR based on RECIST 1.1, and
    - Was treated with at least 8 cycles of study intervention before discontinuing treatment, and
    - Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared

OR

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

AND

- Experienced an investigator-determined radiographic disease progression by RECIST 1.1 after stopping initial treatment, 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.

Participants who have experienced an initial disease progression by RECIST 1.1 and have an iSD, iPR, or iCR per iRECIST after completion of 35 administrations of study intervention for reasons other than disease progression or intolerability may be considered for the Second Course Phase after consultation with the Sponsor.

The decision of whether or not to continue lenvatinib/placebo during Second Course will be at the discretion of the investigator. If continued, participants will be retreated at the same dose level and frequency as when they last received the combination of pembrolizumab and lenvatinib/placebo. Treatment with lenvatinib/placebo will continue until meeting at least 1 of the discontinuation criteria listed in Section 7.1.

An objective response or PD that occurs during Second Course Treatment will not be counted as an event for the primary analyses of either endpoint in this study.

7.2 Participant Withdrawal From the Study

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

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

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

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) 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 providing documented informed consent 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 informed consent from each potential participant or their legally acceptable representative prior to participating in this 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 documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the trial protocol number, trial protocol title, dated signature, and agreement of the participant (or their legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) 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 their 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 or the participant's legally acceptable representative's dated signature.

If the investigator recommends continuation of study intervention beyond disease progression, the participant or their legally acceptable representative will be asked to provide documented informed consent.

Specifics about a the study and the study population are to be included in the study informed consent form.

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 documented 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

8.1.4.1 General Medical History

A medical history will be obtained by the investigator or qualified designee.

Medical history will include all active conditions, drug allergies, significant medical procedures, smoking status, and any condition diagnosed within the previous 10 years that is considered to be clinically important by the investigator. Any cancer, other than the cancer under study, will be recorded as medical history, even if diagnosed greater than 10 years before enrollment. Details regarding the cancer under study will be recorded separately and not listed as medical history.

8.1.4.2 Oncologic Disease Details

The investigator or qualified designee will obtain historic and current details of the participant's cancer under study. This information will include, but is not limited to, date of diagnosis, stage, histology, location(s) of primary lesions, and location(s) of metastases, if applicable.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant

within 30 days prior to the first dose of study intervention. Treatment for the disease for which the participant has enrolled in the study will be recorded separately and not listed as a prior medication.

8.1.5.2 Prior Oncologic Treatment

The investigator or qualified designee will review and record all treatments for the cancer under study, including systemic and local treatment, vaccinations, radiation, and surgeries. Additional information collected on these treatments will include, but is not limited to, reason for discontinuation, best response, and date of progression after each treatment as applicable.

8.1.5.3 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study. Concomitant medications will be recorded for 30 days after the last dose of study intervention (or 90 days if used to treat an SAE).

In addition, medications taken 30 days prior to the first dose of Second Course Treatment, during Second Course Treatment, and for 30 days after the last dose of Second Course Treatment (or 90 days if used to treat an SAE) will be recorded.

Any new anticancer therapy started after the participant's discontinuation from the treatment period will be recorded separately. Additional information collected on this treatment will include, but is not limited to, best response and date of progression.

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/rescreening Visit requirements 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.

The investigator must decide the choice of platinum chemotherapy (carboplatin or cisplatin) and provide the rationale prior to randomization.

8.1.8 Study Intervention Administration

Refer to Section 8.1.8.1 for dose and treatment details. Study intervention should begin within 3 days of randomization.

8.1.8.1 Timing of Dose Administration

8.1.8.1.1 Lenvatinib/Matching Placebo

Lenvatinib/matching placebo 8 mg (two 4-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 each pembrolizumab cycle, lenvatinib/matching placebo will be administered in the clinic 0 to 4 hours after completion of pembrolizumab administration. During chemotherapy cycles (Cycles 1 to 4), lenvatinib/matching placebo will be administered after pembrolizumab and prior to chemotherapy. On Cycle 1 Day 15, lenvatinib is to be administered in the clinic to order to obtain PK samples. 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 by IV infusion over 30 minutes as the first study intervention 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/+10 minutes).

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

8.1.8.1.3 Carboplatin

Participants who will be treated with carboplatin will receive it by IV infusion over 15-60 minutes (or per approved local label guidelines) after pemetrexed on Day 1 of each 21-day cycle. Participants should also receive premedication per the approved product label.

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

8.1.8.1.4 Cisplatin

Participants who will be treated with cisplatin will receive it by IV infusion over 60 minutes (or per approved local label guidelines) after pemetrexed on Day 1 of each 21-day cycle. Participants should also receive premedication per the approved product label.

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

8.1.8.1.5 Pemetrexed

Pemetrexed will be administered by IV infusion over 10 minutes (or per approved local label guidelines) on Day 1 of each 21-day cycle. Pemetrexed should be administered prior to carboplatin or cisplatin during those treatment cycles. Participants should receive premedication per the approved product label.

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

8.1.8.2 Treatment Compliance

8.1.8.2.1 Lenvatinib/Placebo

During on-site visits, administration of lenvatinib/placebo will be monitored by the investigator and/or study staff. The administration, the dose, the time of administration, as well as any immediate reactions at the time of intake will be documented in the electronic Case Report Form (eCRF).

On all other days, lenvatinib/placebo will be taken at home. When a participant attends a study visit, he or she will bring any unused tablets.

8.1.8.2.2 Pembrolizumab/Platinum Doublet Chemotherapy

Administration of pembrolizumab and platinum doublet chemotherapy will be monitored by the investigator and/or study staff. The total volume of study intervention infused will be compared with the total volume prepared to determine compliance with each dose administered.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.11.3.

When a participant withdraws from participation in the study, all applicable activities scheduled for the End of Treatment Visit should be performed (at the time of withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.3.

8.1.10 Participant Blinding/Unblinding

As of the final analysis, the study was unblinded. Original protocol text that is contained in this section has been retained for reference.

Part 1 (safety run-in) of the study will be unblinded, open-label.

In Part 2 (Phase 3 study), STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity/toxicity grade of the AEs observed, the relation to study intervention, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor's Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

The IRT system should be used for emergency unblinding in the event that this is required for participant safety.

At the end of the study, random code/disclosure envelopes or lists and unblinding logs are to be returned to the Sponsor or designee.

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 Assessments

8.2.1 Tumor Scans and Response Assessment

As of Amendment 08, participants who are still on study treatment will no longer require tumor response assessments by BICR to be performed. Scans will no longer be submitted to

the iCRO. Participants who are still on study medication should continue tumor imaging assessment as assessed by investigator per protocol. Original protocol text that is contained in this section has been retained for reference.

Throughout this section, the term "scan" refers to any medical imaging data used to assess tumor burden and may include cross-sectional imaging (such as CT or MRI), medical photography, or other methods as specified in this protocol.

The process for scan collection and transmission to the central imaging vendor can be found in the Site Imaging Manual. Tumor scans by CT is strongly preferred. For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. MRI is the strongly preferred modality for brain scans. The same scan 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 scans. Note: For the purposes of assessing tumor scans, the term "investigator" refers to the local investigator at the site and/or the radiological reviewer located at the site or at an offsite facility.

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

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). In clinically stable participants, scans should continue until PD has been verified. Once PD is verified centrally, subsequent scans (if acquired) should not be submitted to the central imaging vendor.

8.2.1.1 Initial Tumor Scans

Initial tumor scans at Screening must be performed within 28 days prior to the date of randomization. Any scans obtained after Cycle 1 Day 1 of treatment cannot be included in the screening assessment. The site study team must review screening scans to confirm the participant has measurable disease per RECIST 1.1.

The screening scans must be submitted to the central imaging vendor for retrospective review.

Tumor scans performed as part of routine clinical management are acceptable for use as screening tumor scans if they are of diagnostic quality, performed within 28 days prior to the date of randomization, and can be assessed by the central imaging vendor.

If brain scan 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.

8.2.1.2 Tumor Scans During the Study

The first on-study scan assessment should be performed at 6 weeks (+7 days) from the day of randomization. Subsequent tumor scans should be performed every 6 weeks (±7 days) until Week 18, and every 9 weeks (±7 days) or more frequently if clinically indicated. After 54 weeks, participants who remain on treatment will have scans performed every 12 weeks (±7 days). Scan timing should follow calendar days and should not be adjusted for delays in cycle starts. Scans should continue to be performed until disease progression is documented radiographically per RECIST 1.1 and verified by BICR (unless the investigator elects to continue treatment and follow iRECIST), initiating a new anticancer therapy, participant withdrawal of consent, pregnancy, becoming lost to follow-up, death, or the end of the study, whichever is earlier.

All supplemental scans must be submitted to the central imaging vendor.

Objective response should be confirmed by a repeat scan assessment. Tumor scans 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 scans, starting with the next scheduled scan time point. Participants who receive additional scans for confirmation do not need to undergo the next scheduled tumor scan if it is less than 4 weeks later; tumor scans may resume at the subsequent scheduled scan 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 PD 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 scans do not need to undergo the next scheduled tumor scan if it is less than 4 weeks later; tumor scans may resume at the subsequent scheduled scan time point, if clinically stable. Participants who have confirmed PD by iRECIST, as assessed by the site, will discontinue study intervention. Exceptions are detailed in Section 8.2.1.6.

8.2.1.3 End of Treatment and Follow-up Tumor Scans

Follow-up tumor imaging is only required for participants who are candidate for Second Course treatment.

For participants who discontinue study intervention, tumor scans should be performed at the time of treatment discontinuation (±4 weeks). If previous scans were obtained within 4 weeks before the date of discontinuation, then scans at treatment discontinuation are not mandatory. For participants who discontinue study intervention because of documented disease

progression, this is the final required tumor scan 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 scans using the same scan schedule used while on treatment (every 6 weeks until Week 18, every 9 weeks until Week 54, and then every 12 weeks) until disease progression is documented radiographically per RECIST 1.1 and verified by BICR (unless the investigator elects to continue treatment and follow iRECIST), initiating a new anticancer therapy, participant withdrawal of consent, pregnancy, becoming lost to follow-up, death, or the end of the study, whichever is earlier.

8.2.1.4 Second Course Treatment Tumor Scans

Before a participant may enter the Second Course Phase, BICR-verification of radiographic disease progression must have occurred. Tumor scans must be performed within 30 days before the first Second Course Treatment. The disease progression scans may also be used as the Second Course baseline scans if it is within 30 days before restarting treatment and otherwise meets the baseline standards outlined in the Site Imaging Manual. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility. All Second Course Treatment scans should be submitted to the central imaging vendor for quality control, storage, and possible retrospective review. The first on-study scan assessment during Second Course Treatment should be performed at 12 weeks (±7 days) after the restart of treatment. Subsequent tumor scans should be performed every 12 weeks (±7 days) or more frequently, if clinically indicated. Scan timing should follow calendar days and should not be adjusted for delays in cycle starts.

Per iRECIST (Section 8.2.1.6), if tumor scans show 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 scans do not need to undergo scheduled tumor scans if it is less than 4 weeks later and may wait until the next scheduled scan time point, if clinically stable.

Scans should continue to be performed until disease progression, initiating a new anticancer therapy, participant withdrawal of consent, pregnancy, becoming lost to follow-up, death, or the end of the study, whichever is earlier. In clinically stable participants, PD may be confirmed by the investigator using iRECIST 4 to 8 weeks after the first tumor scan indicating PD.

For participants who discontinue Second Course Treatment, tumor scans should be performed at the time of treatment discontinuation (±4 weeks). If previous scans were obtained within 4 weeks before the date of discontinuation, then scans at treatment discontinuation are not mandatory. For participants who discontinue study intervention because of documented disease progression, this is the final required tumor scan.

For participants who discontinue Second Course Treatment without documented disease progression, every effort should be made to continue monitoring their disease status by

radiologic scans every 12 weeks (±7 days) until disease progression, initiating a new anticancer therapy, participant withdrawal of consent, pregnancy, becoming lost to follow-up, death, or the end of the study, whichever is earlier.

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). Initial tumor scans showing site-assessed PD should be submitted immediately for BICR verification of disease progression. The site will be notified if the BICR verifies disease progression using RECIST 1.1. Figure 2 illustrates the scan flow involving verification of disease progression for clinically stable participants.

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

- If participant is clinically stable, continue study intervention per protocol
  - Resume scans per protocol schedule (≥4 weeks to next scan)
  - Send scans to central imaging vendor
  - Continue local assessment
  - Do not change investigator assessment of progression
  - If subsequent scan(s) indicate progression, submit scan(s) to central imaging vendor to request verification
- If the participant is not clinically stable, best medical practice is to be applied

Before stopping study intervention or scans or starting new anticancer therapy in a participant who is clinically stable, communication with the Sponsor is required.

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, communication with the Sponsor is required and a reconsent addendum must be signed
- Obtain scans locally per original protocol schedule
- Do not send scans to central imaging vendor

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

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 disease progression is confirmed by the investigator, working with local radiology. This allowance to continue treatment despite initial radiologic disease progression 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 disease progression
- No decline in ECOG performance status
- No requirement for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed clinically unstable should be discontinued from study intervention at site-assessed first radiologic evidence of disease progression and is not required to have repeat tumor scans for confirmation of disease progression 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 disease progression by iRECIST, per investigator assessment. Scans should continue to be sent in to the central imaging vendor for potential retrospective BICR.

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

If a participant has iRECIST-confirmed radiographic progression (iCPD), study intervention should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study intervention may be considered following consultation with the Sponsor. In this case, if study intervention is continued, tumor scans should continue to be performed following the intervals outlined in Section 1.3 and submitted to the central imaging vendor.

A description of the adaptations and iRECIST process is provided in Appendix 6, with additional details in the iRECIST publication [Seymour, L., et al 2017]. A summary of scans and treatment requirements after first radiologic evidence of progression is provided in Table 10 and illustrated as a flowchart in Figure 2.

Table 10 Summary of Imaging and Treatment Requirements After First Radiologic Evidence of Disease Progression

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1 that has been verified by BICR	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 at the investigator's discretion only.	Discontinue 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 at the 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 intervention at the investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study intervention if condition has improved and/or clinically stable at the 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 = modification of 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 central imaging vendor, but no rapid review will occur. If RECIST 1.1 PD has not been centrally verified, ideally the site should continue treatment. Whether or not treatment continues, imaging should be collected and submitted to the central imaging vendor with VOP request until RECIST 1.1 PD is verified by BICR.

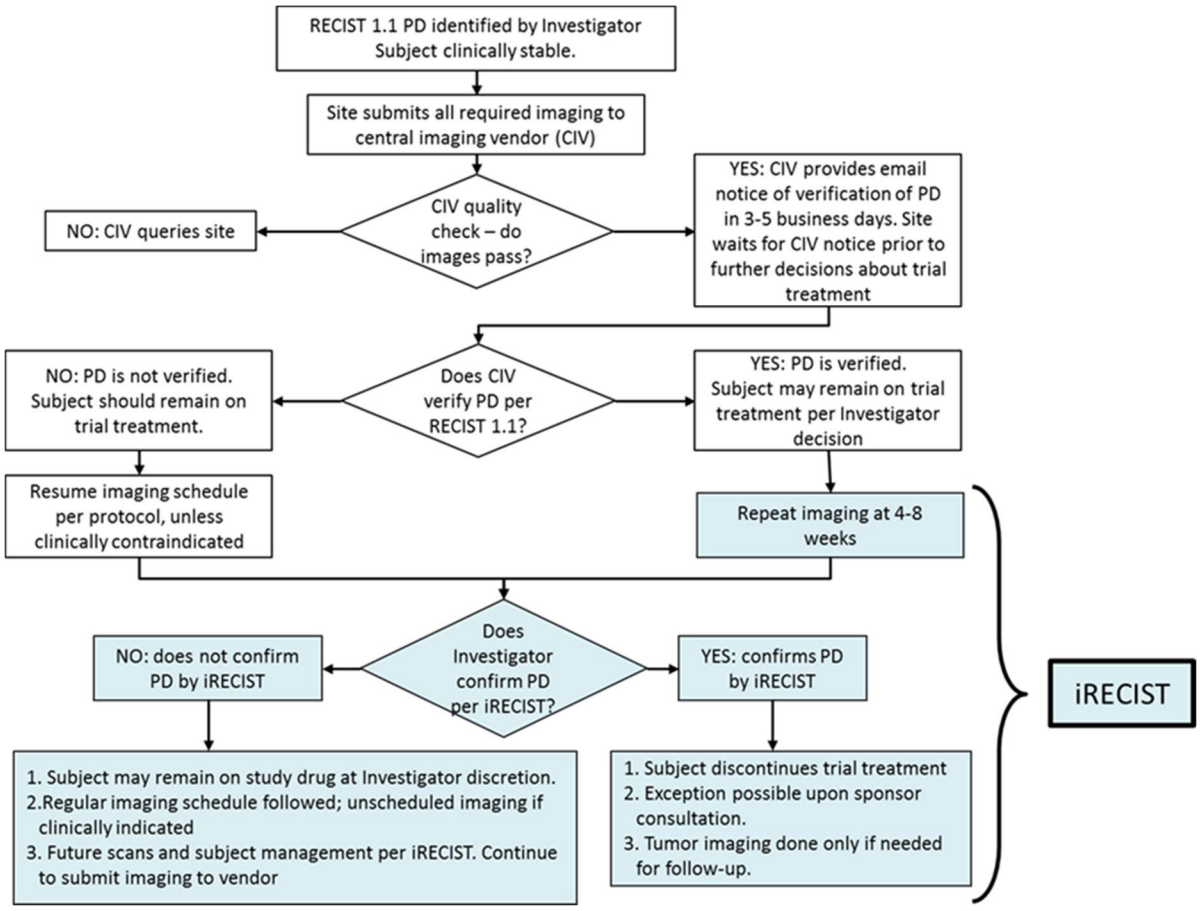


Figure 2 Imaging and Treatment for Clinically Stable Participants After First Radiologic Evidence of Progressive Disease Assessed by the Investigator

8.2.1.7 Tumor Tissue Collection for Biomarker Analysis

Participation in this study will be dependent upon supplying tumor tissue for biomarker testing from locations not radiated before biopsy. Formalin-fixed specimens after the participant has been diagnosed with metastatic disease but before randomization are preferred. Biopsies obtained before receipt of adjuvant/neoadjuvant chemotherapy are permitted if recent biopsy is not feasible.

All participants should submit either a newly obtained core or excisional biopsy or archival tissue (fine-needle aspiration is not adequate for either archival or new tissue samples) to a central laboratory for biomarker analysis.

Note: Submission of FFPE tumor tissue sample blocks are preferred; if submitting unstained slides, the slides should be freshly cut and submitted to the testing laboratory within 14 days from the site slide section date; otherwise, a new specimen will be requested.

If the sample is determined to be nonevaluable before testing by the central laboratory, a new sample should be submitted if available.

8.2.2 Patient-Reported Outcomes

As of Amendment 08, participants who are still on study treatment will no longer require ePRO assessments. Original protocol text that is contained in this section has been retained for reference.

The EORTC QLQ-C30, EORTC QLQ-LC13, and EuroQoL EQ-5D-5L questionnaires will be administered by trained site personnel and completed electronically by participants in the following order: EORTC QLQ-C30 first, then EORTC QLQ-LC13, then EuroQoL EQ-5D-5L. It is best practice and strongly recommended that electronic PROs (ePROs) be administered to randomized participants prior to study intervention administration, AE evaluation, and disease status notification. If the ePROs are not done at a scheduled time point, the MISS_MODE form must be completed to capture the reason the assessment was not performed.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

The investigator or qualified designee will perform a full physical examination including oral examination during the Screening period and as indicated in the SoA. Clinically significant abnormal findings at Screening should be recorded as medical history. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

For cycles that do not require a full physical examination per the SoA (Section 1.3), the investigator or qualified designee will perform a directed physical examination including oral examination as clinically indicated.

During the treatment period, physical examinations should be performed prior to dosing. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital Signs

The investigator or qualified designee will take vital signs at Screening, before the administration of each dose of study treatment and during the Follow-up Period, as specified in the SoA (Section 1.3). Vital signs include temperature, heart rate, respiratory rate, weight, and BP. Height will be measured at Screening only.

- 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 BR <90 mm Hg. If the participant's initial BP 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) shows an elevated BP (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

- Under exceptional circumstances, participants will have the option of having BP measured between visits obtained locally by a health care professional. A diary will be provided as a tool to aid the participant in collecting BP evaluations between study visits.

8.3.3 Electrocardiograms

Electrocardiograms (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.

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

QTc prolongation has been seen in some lenvatinib studies. Monitor electrocardiograms every cycle (as specified in the Schedule of Assessments) in patients 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.

8.3.4 Echocardiograms or Multigated Acquisition Scans

A MUGA scan (using a technetium-based tracer) or an ECHO will be performed to assess LVEF.

MUGA scans or ECHOs 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.

LVEF, as assessed by the institution, will be entered in the eCRF. Investigator assessment will be based on institutional reports.

8.3.5 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2.

8.3.6 Pregnancy Test

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 of the first dose of study intervention. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study in the event of a positive test result. Repeated pregnancy test (such as monthly testing) may be conducted if required by local regulation.

8.3.7 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 (90 days if considered an SAE) 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 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 participant provides documented informed consent 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 30 days following cessation of study intervention must be reported by the investigator.

- All AEs meeting serious criteria, from the time of intervention allocation/randomization through 90 days following cessation of study intervention or 30 days following 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 the last dose of pembrolizumab and/or 30 days after lenvatinib/matching placebo, 180 days after last dose of chemotherapeutic agents, or 30 days after the last doses of these agents if the participant initiates new anticancer therapy in that timeframe.

- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered drug-related.

- Country-specific requirements are listed in Appendix 7.

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.

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 11.

Participants who enter the separate Extension Study:

From the time of intervention randomization through 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 parent study will be collected in the parent study.

Note: Once consented to the extension study, AEs and other reportable events meeting the criteria of the extension study, including those considered related to study intervention, will be collected in the extension study.

Table 11 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:**
Nonserious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all SAEs, cancer, overdose associated with pembrolizumab and overdose associated with lenvatinib with an AE	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event

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:**
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

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

Care will be taken not to introduce bias when detecting 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 (eg, 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 Section 3 will not be reported to the Sponsor as AEs/SAEs. Specifically, the suspected/actual events covered in this exception include any event that is progression of the cancer under study.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the participants in the study. Any suspected endpoint that upon review is

not progression of the cancer under study will be forwarded to Global Pharmacovigilance as an SAE within 24 hours of determination that the event is not progression of the cancer under study.

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:

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

2. Any dose over the prescribed dose of lenvatinib associated with an AE.

3. 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: any dose 1000 mg or greater

- Lenvatinib: any dose above the protocol-prescribed dose if associated with an adverse event

There is no specific antidote for an overdose of lenvatinib. Due to its high degree of plasma protein binding, lenvatinib is not expected to be dialyzable. Adverse reactions in patients receiving single doses of lenvatinib as high as 40 mg were similar to those in clinical studies at the recommended dose for DTC and RCC.

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

If an AE(s) is associated with ("results from") the overdose of pembrolizumab, the AE(s) is reported as an SAE, even if no other seriousness criteria are met. Overdoses associated with

lenvatinib should be reported as a nonserious Event of Clinical Interest (ECI), unless the AE itself meets criteria for an SAE.

If a dose of pembrolizumab meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a nonserious ECI, using the terminology "accidental or intentional overdose without adverse effect."

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

For chemotherapy, please refer to the local label for the definition of overdose.

8.6 Pharmacokinetics

As of Amendment 08, participants who are still on study treatment will no longer require PK assessments. Original protocol text that is contained in this section has been retained for reference.

8.6.1 Blood Collection for Lenvatinib

Blood samples will be collected as specified in the SoA (Section 1.3). Study sites must have appropriately trained staff and adequate equipment for procuring and processing specimens. Instructions for the collection, handling, and shipping procedures of PK samples will be provided in the Laboratory Manual.

Blood samples will be collected from all participants. Plasma concentrations of lenvatinib when co-administered with pembrolizumab will be measured. Lenvatinib will be analyzed using a population PK approach.

If at some point during the study, prospective PK blood sample collection is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued, and sites will be notified accordingly.

8.6.2 Blood Collection for Pembrolizumab

To evaluate pembrolizumab immunogenicity and exposure when administered in combination with lenvatinib, sample collections for analysis of antidrug antibodies (ADAs) and PK are currently planned as specified in the SoA (Section 1.3). Study sites must have appropriately trained staff and adequate equipment for procuring and processing specimens. Instructions for the collection, handling, and shipping procedures of ADA and PK samples will be provided in the Laboratory Manual.

Blood samples for pembrolizumab PK and ADA collected may only be stored at this time. Further analysis may be performed if required and reported separately if conducted. If ongoing PK and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

8.6.3 Blood Collection for Chemotherapy

Blood samples will be collected as specified in the SoA (Section 1.3). Study sites must have appropriately trained staff and adequate equipment for procuring and processing specimens. Instructions for the collection, handling, and shipping procedures of PK samples will be provided in the Laboratory Manual.

Blood samples for chemotherapy PK collected may only be stored at this time. Further analysis may be performed if required and reported separately if conducted.

If ongoing PK sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

8.7 Pharmacodynamics

Not applicable.

8.8 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/IEC does not approve) sample collection for these purposes, then such samples should not be collected at the corresponding sites.

8.9 Biomarkers

As of Amendment 08, participants who are still on study treatment will no longer require biomarker assessments. Original protocol text that is contained in this section has been retained for reference.

To identify novel biomarkers, the following biospecimens to support exploratory analysis of cellular components (eg, protein, RNA, DNA, metabolites) and other circulating molecules will be collected from all participants as specified in the SoA:

- Blood for genetic analysis
- Blood for RNA analysis
- Blood for serum biomarkers
- Blood for plasma biomarkers
- Blood for serum biomarkers
- Blood for circulating tumor nucleic acids
- Newly Obtained/Archival Tissue Sample for Biomarker Analysis

Sample collection, storage, and shipment instructions for exploratory biomarker specimens will be provided in the operations/laboratory manual.

8.10 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data associated with medical encounters, excluding protocol-mandated procedures, tests, and encounters, will be collected in the eCRF by the investigator and study site personnel for all participants.

The data collected may be used to conduct exploratory economic analyses.

All-cause hospitalizations and emergency room visits must be reported in the eCRF from the time of randomization through 90 days after the last dose of study intervention, or 30 days after the last dose of study intervention if the participant initiates a new anticancer therapy, whichever is earlier.

8.11 Treatment Eligibility Assessment

The investigator must complete the eCRF and provide rationale to document the choice of (or potential treatment with) cisplatin prior to randomization.

8.12 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8. Unscheduled visits are permitted at any time during the course of the study.

8.12.1 Screening Period

Documented informed consent must be provided before performing any protocol-specific procedure. Results of a test performed before the participant signs the ICF 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 before the first dose of study intervention except for the following:

- Full physical examination at Screening should be performed within 7 days prior to Cycle 1 Day 1.
- Evaluation of ECOG at Screening should be performed within 7 days prior to Cycle 1 Day 1 but before randomization.
- For WOCBP, a urine or serum pregnancy test will be performed within 72 hours prior to the first dose of study intervention. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required (performed by the local study site laboratory).

- Laboratory tests at Screening should be performed within 10 days prior to Cycle 1 Day 1.

- Urinalysis at Screening should be performed within 7 days prior to Cycle 1 Day 1.

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 are met. Participants who are rescreened will retain their original screening number.

8.12.2 Treatment Period

In Part 1 (safety run-in), participants who are eligible for study participation will be assigned to receive unblinded, open-label treatment with lenvatinib + pembrolizumab + platinum doublet chemotherapy.

In Part 2 (Phase 3 study), participants who are eligible for study participation will be randomly assigned to receive lenvatinib + pembrolizumab + platinum doublet chemotherapy (Arm 1) or matching placebo + pembrolizumab + platinum doublet chemotherapy (Arm 2).

Lenvatinib/matching placebo will be taken orally once daily, and pembrolizumab and platinum doublet chemotherapy will be given by IV infusion on Day 1 of each 21-day cycle, as outlined in Section 8.1.8.

In Cycles 1 and 2, study visits will occur on Days 1 and 15. Participants will be contacted by telephone on Cycle 1, Day 8. Beginning in Cycle 3, participants will be required to attend study visits on Day 1 only. Participants may be seen more frequently, if clinically indicated. Tumor scans and response assessment will occur every 6 weeks from the day of randomization until Week 18, followed by every 9 weeks until Week 54, and every 12 weeks thereafter.

Study interventions will continue until reaching a discontinuation criterion (Section 7.1), examples of which include disease progression which is radiographically documented per RECIST 1.1, and only when clinically appropriate, confirmed by the site per iRECIST; unacceptable toxicity; intercurrent illness that prevents further administration of treatment; investigator's decision to withdraw treatment; participant withdrawal of consent; pregnancy; noncompliance with study intervention or procedure requirements; administrative reasons requiring cessation of treatment; or, for carboplatin, cisplatin, and pembrolizumab ONLY, treatment completion (4 cycles of carboplatin or cisplatin/35 cycles of pembrolizumab). There is no treatment duration limit for lenvatinib/matching placebo or pemetrexed.

Participants treated with pembrolizumab who complete 35 cycles of treatment with SD or better or participants who attain an investigator-determined CR and have received at least 8 cycles of pembrolizumab may be eligible for Second Course Treatment as outlined in Section 7.1.1.

8.12.3 Discontinued Participants Continuing to be Monitored in the Study

The Discontinuation Visit should occur at the time study intervention is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study intervention, at the time of the mandatory Safety Follow-up visit, the Discontinuation Visit procedures and any additional Safety Follow-up procedures should be performed.

Visit requirements are outlined in the SoA. Additional details regarding participant withdrawal and discontinuation are presented in Section 8.1.9.

8.12.4 Posttreatment Period

8.12.4.1 Safety Follow-up Visit

The 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 therapy, whichever is earlier.

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

8.12.4.2 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than PD will move into Efficacy Follow-up and should be assessed as outlined in the SoA (Section 1.3) to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, PD, death, or end of study, or if the participant begins retreatment with pembrolizumab, as detailed in Section 8.11.2. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter Survival Follow-up.

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 8.11.2 will move from Efficacy Follow-up to Second Course Treatment when they experience PD. Details are provided in the SoA (Section 1.3) for retreatment with pembrolizumab

8.12.4.3 Survival Follow-up Visits

Participant survival status will be assessed approximately every 12 weeks until death, withdrawal of consent, or the end of the study, whichever occurs first. Participants may be contacted for survival status at any time during the course of the study.

For participants who discontinue treatment intervention and who will not enter Efficacy Follow-up, the first Survival Follow-up assessment will be scheduled 12 weeks after the Discontinuation Visit and/or Safety Follow-up Visit (whichever is last).

For participants who completed assessments in Efficacy Follow-up, the first Survival Follow-up assessment will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If changes are made to primary and/or key secondary hypotheses or the statistical methods related to those hypotheses after the study has begun, but prior to any unblinding/final database lock, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to unblinding/final database lock, will be documented in a supplemental statistical analysis plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. Separate analysis plans (ie, separate documents from the sSAP) may be developed to detail PK and biomarker analyses. The PRO analysis plan will be included in the sSAP.

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Phase 3 study of platinum doublet chemotherapy + pembrolizumab with or without lenvatinib as first-line treatment in patients with treatment-naïve, metastatic nonsquamous NSCLC.
Treatment Assignment	Part 1: Approximately 12 to 20 participants will be assigned to one of 2 treatment arms, at the discretion of the investigator, until at least 6 participants are treated per arm: 1. Lenvatinib + pembrolizumab + carboplatin + pemetrexed 2. Lenvatinib + pembrolizumab + cisplatin + pemetrexed Part 2: Approximately 714 participants will be randomized in a 1:1 ratio to one of 2 treatment arms: 1. Lenvatinib + platinum doublet chemotherapy + pembrolizumab 2. Placebo + platinum doublet chemotherapy + pembrolizumab Stratification factors for Part 2 are as follows: • PD-L1 TPS: <50% vs. ≥50% • Geography site: East Asian vs. non-East Asian • ECOG performance status: 0 vs. 1
Analysis Populations	Part 1 and Part 2 participants will be analyzed separately. Efficacy: Intention-to-Treat (ITT) Safety: All-Participants-as-Treated (APaT)
Primary Endpoints	Part 1: Safety and tolerability Part 2: • Progression-free Survival (PFS) per RECIST 1.1 assessed by BICR • Overall Survival (OS)

Secondary Endpoints	Part 2: • Objective response per RECIST 1.1 based on BICR • DOR per RECIST 1.1 based on BICR • Safety and tolerability • Change from baseline in Global health status/QoL, cough, chest pain, dyspnea, and physical functioning scores • TTD in global health status/QoL, cough, chest pain, dyspnea, and physical functioning • TTD in the composite endpoint of cough, chest pain, or dyspnea items
Statistical Methods for Key Efficacy Analyses	Part 2: The dual primary hypotheses of PFS and OS will be evaluated by comparing lenvatinib to placebo in combination with platinum doublet chemotherapy and pembrolizumab using a stratified log-rank test. The hazard ratio (HR) will be estimated using a stratified Cox regression model. Event rates over time will be estimated within each treatment arm using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	Part 1: Descriptive summary statistics will be provided for safety endpoints by treatment as appropriate. Part 2: The analysis of safety results will follow a tiered approach. There are no events of interest that warrant elevation to Tier 1 events in this study. All safety parameters are considered either Tier 2 or Tier 3. Tier 2 safety parameters will be assessed via point estimates with 95% confidence intervals (CIs) provided for between-treatment comparisons. Tier 3 safety parameters will be assessed only via point estimates by treatment. Between-treatment differences will be analyzed using the Miettinen and Nurminen method.
Interim Analyses	**Part 1**: No formal interim analysis is planned. Participants will be closely followed for DLTs for 21 days after the first dose of study intervention. **Part 2 Efficacy**: Four analyses are planned for this study: 3 interim analyses and 1 final analysis. Results from the first 3 interim analyses will be reviewed by an external Data Monitoring Committee. Details are provided in Section 9.7. Interim analysis 1 (IA1) • Timing: To be performed after ~ 420 participants are randomized with at least 9 months of follow-up (ie, ~ 19 months after study start) • Primary purpose: efficacy analysis for ORR Interim analysis 2 (IA2) • Timing: To be performed after both ~ 420 PFS events have been observed and ~8 months after last participant randomized • Primary purpose: efficacy analysis for PFS and OS Interim analysis 3 (IA3) • Timing: To be performed after both ~ 480 PFS events have been observed and ~18 months after last participant randomized • Primary purpose: efficacy analysis for PFS and OS Final Analysis (FA) • Timing: To be performed after both ~ 445 OS events have been observed and ~29 months after last participant randomized • Primary purpose: efficacy analysis for OS

	Note that for IA2, IA3 and FA, if the PFS (for IA2 and IA3) or OS (for FA) events accrue slower than expected, the Sponsor may conduct the analysis with additional 2 months of follow-up, or the specified number of events is observed, whichever occurs first. **Part 2 Safety**: An interim safety analysis will be performed and reviewed by the eDMC after at least 40 participants (~ 10 participants treated with carboplatin in each treatment arm and ~ 10 participants treated with cisplatin in each treatment arm) complete at least 2 cycles of treatment. Afterwards, the eDMC will review safety data periodically in the study. Details will be specified in the DMC Charter.
Multiplicity	Part 1: No multiplicity adjustment is planned. Part 2: The overall Type I error over the primary and secondary hypotheses is strongly controlled at 2.5% (1-sided), with 0.1% initially allocated to ORR, 0.5% to PFS, and 1.9% to OS. By using the graphical approach of Maurer and Bretz, if one hypothesis is rejected, the alpha will be shifted to other hypotheses.
Sample Size and Power	Part 1: Approximately 12 to 20 participants will be enrolled. Part 2: The planned sample size is approximately 714 participants with approximately 357 participants in each treatment arm. There will be ~420 participants randomized with at least 9 months of follow-up at the ORR final analysis. The study has ~83% power for detecting a 20% point difference between treatment arms with an underlying 48% response rate in the control arm at an initially assigned 0.001 (1-sided) significance level. It is estimated that there will be ~ 480 events at the PFS final analysis (ie, IA3 of the study). With 480 PFS events, the study has ~90% power for detecting a HR of 0.7 at an initially assigned 0.005 (1-sided) significance level. It is estimated that there will be ~ 445 deaths at the OS final analysis. With 445 deaths, the study has ~90% power for detecting a HR of 0.725 at an initially assigned 0.019 (1-sided) significance level.
China Extension Study	China participants randomized during the global study phase will be included in all global study analyses (efficacy and safety). China participants randomized during the China extension phase will be excluded from all global study analyses. China participants randomized during global and extension phases will both be included in the China-specific analyses.

9.2 Responsibility for Analyses/In-house Blinding

Statistical analyses of the data obtained from this study will be the responsibility of the Sponsor's Clinical Biostatistics department.

Part 1 of the study is being conducted as an open-label study, ie, participants, investigators, and Sponsor personnel will be aware of treatment assignments after each participant is enrolled and treatment is assigned. Safety data will be closely monitored for 21 days after the first dose of study intervention.

Part 2 of the study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

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

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

Extension Study in China

For all participants in China, including participants randomized in the global study and the extension study, participant level treatment randomization information will be blinded to the statistician(s)/programmer(s) responsible for the analysis of the Extension Study in China until the extension study database lock is achieved. The extent to which individuals are unblinded to the results will be limited. Blinded and unblinded members will be clearly documented.

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for between-treatment arm differences are listed below.

9.4.1 Efficacy Endpoints

Primary Endpoints

Progression-free survival (PFS) using RECIST 1.1 assessed by BICR: PFS is defined as the time from randomization to the date of the first documentation of disease progression, as determined by BICR per RECIST 1.1, or death from any cause, whichever is earlier. See Section 9.6.1 for the definitions of censoring.

Overall Survival (OS): OS is defined as the time from randomization to the date of death from any cause.

Secondary Endpoints

Objective response using RECIST 1.1 assessed by BICR: Objective response is a confirmed complete response (CR) or partial response (PR), as determined by BICR per RECIST 1.1.

Duration of Response (DOR) using RECIST 1.1 assessed by BICR: DOR is defined as the time from the first documented evidence of CR or PR until disease progression or death due to any cause (whichever is earlier), for participants who demonstrate a confirmed CR or PR. Response will be determined by BICR per RECIST 1.1.

9.4.2 Safety Endpoints

Dose-limiting toxicities for Part 1 are defined in Table 1. Other safety measurements for all participants are described in Section 8.3 and Section 8.4 and include AEs, SAEs, fatal AEs, laboratory test results, vital sign results, and ECG results. Furthermore, specific events will be collected and designated as ECIs as described in Section 8.4.7.

9.4.3 Patient-reported Endpoints

The following secondary PRO endpoints will be evaluated as described in Section 4.2.1.3 and analyzed as described in Section 9.6.3:

Change from baseline in

- Global Health Status/QoL scale (QLQ-C30 items 29 and 30)
- Single-item symptom scales: cough (QLQ-LC13 item 31), chest pain (QLQ-LC13 item 40), and dyspnea (QLQ-C30 item 8)
- Physical functioning scale (QLQ-C30 items 1-5)

Time to true deterioration (TTD) in

- Global Health Status/QoL scale (QLQ-C30 items 29-30)
- Single-item symptom scales: cough (QLQ-LC13 item 31), chest pain (QLQ-LC13 item 40), and dyspnea (QLQ-C30 item 8)
- Physical functioning scale (QLQ-C30 items 1-5)
- Composite symptom endpoint: cough (QLQ-LC13 Item 31), chest pain (QLQ-LC13 Item 40), and dyspnea (QLQ-C30 Item 8)

The TTD in global health status/QoL, cough, chest pain, dyspnea, and physical functioning is defined as the time from baseline to the first onset of a 10 or more points deterioration from baseline with confirmation by the subsequent visit of a 10 or more points deterioration from baseline. The TTD in the composite endpoint of cough, chest pain, or dyspnea is defined as the time to first onset of 10 or more points deterioration from baseline in any one of 3 scale items with confirmation by the subsequent visit of 10 points or more deterioration from baseline in the same scale as the first onset. The EQ-5D-5L will be evaluated as an exploratory endpoint. These analyses and other supportive PRO analyses will be described in the sSAP.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The ITT population will serve as the population for primary efficacy analyses. All randomized participants will be included in this population. Participants will be analyzed in the treatment arm to which they were randomized.

Part 1 participants will be excluded from all Part 2 efficacy analyses and therefore will not contribute to the analyses to assess the primary/secondary objectives of Part 2.

Details on the approach to handling missing data are provided in Section 9.6.

Extension Study in China

After enrollment of the global study is closed, the study will continue to randomize participants in China until the sample size for participants in China reaches approximately 200. The participants in China who are randomized in the extension study will not be included in the primary efficacy analysis population for the global study. The China ITT population, including all participants in China randomized in the global study and the extension study, will be analyzed separately.

9.5.2 Safety Analysis Populations

The APaT population will be used for the analysis of safety data in this study. The APaT population will consist of all enrolled (Part 1) and all randomized (Part 2) participants who received at least 1 dose of study intervention. Participants will be included in the treatment arm corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. For most participants this will be the treatment arm to which they were randomized. Participants who take incorrect study intervention for the entire treatment period will be included in the treatment arm corresponding to the study intervention actually received. Any participant who receives incorrect study intervention for 1 cycle but receives the correct treatment for all other cycles will be analyzed according to the correct (ie, randomized) treatment arm and a narrative will be provided for any events that occurred during the cycle for which the participant was incorrectly dosed.

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

Participants in Part 1 and Part 2 will be analyzed separately.

Extension Study in China

The participants in China randomized and treated in the extension study after completion of the global enrollment will not be included in the primary safety analysis population for the global study. The China APaT population, including all participants in China randomized in

the global study and the extension study who received at least 1 dose of study treatment, will be analyzed separately.

9.5.3 PRO Analysis Population

The PRO Full Analysis Set (FAS) population will be used for the analysis of PRO data in this study. The PRO FAS population will consist of all randomized participants who have at least 1 PRO assessment available and have received at least 1 dose of study intervention.

PRO analyses will be performed in Part 2 participants only.

9.5.4 Pharmacokinetic Analysis Population

The Population PK Analysis Set will be used for the analysis of PK data in this study. The Population PK Analysis Set will include all participants who received at least 1 dose of study intervention with documented dosing history in the lenvatinib plus pembrolizumab and chemotherapy treatment arm and have measurable plasma levels of lenvatinib and/or serum levels of pembrolizumab.

PK analyses will be performed using PK data from participants in Part 1 and Part 2 combined.

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

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

Efficacy analyses will be performed in Part 2 participants only. Efficacy results that are 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.

All statistical inferential tests, unless otherwise specified, will be stratified for the stratification factors used in randomization (See Section 6.3.2). In the event that 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, and decisions regarding the pooling will be based on a blinded review of response and event counts by stratum.

The efficacy analyses for ORR, DOR and PFS will include responses and documented progression events that occur prior to Second Course Treatment.

9.6.1.1 Progression-free Survival

The nonparametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment arm. Treatment differences in PFS will be assessed by the stratified log-rank test (based on the stratification factors outlined 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) 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 PD will be approximated by the earlier of the date of the first assessment at which PD is objectively documented per RECIST 1.1 by BICR and the date of death. Death is always considered a PD event.

For the primary analysis, any participant who experiences an event (PD or death) immediately after 2 or more missed disease assessments will be censored at the last disease assessment prior to the missed visits. In addition, any participant who initiates new anticancer therapy prior to documented PD will be censored at the last disease assessment prior to the initiation of new anticancer therapy. Participants who do not start new anticancer therapy and who do not experience an event will be censored at the last disease assessment. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. Sensitivity analyses will be performed for comparison of PFS based on investigator's assessment.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by BICR, two sensitivity analyses with a different set of censoring rules will be performed. The first sensitivity analysis follows intention-to-treat principles. That is, disease progressions/deaths are counted as events regardless of missed study visits or initiation of new anticancer therapy. The second sensitivity analysis considers discontinuation of treatment or initiation of a new anticancer therapy subsequent to discontinuation of study-specified treatments, whichever is later, to be a disease progression event for participants without documented disease progression 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 12.

Table 12 Censoring Rules for Primary and Sensitivity Analyses of Progression-free Survival

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No PD and no death; and new anticancer therapy 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 treatment or completed study treatment
No PD and no death; new anticancer therapy is initiated	Censored at last disease assessment before new anticancer therapy	Censored at last disease assessment	Progressed at date of new anticancer therapy
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
Death or progression immediately after ≥2 consecutive missed disease assessments, or after new anticancer therapy	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessments and new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
Abbreviation: PD = progressive disease			

9.6.1.2 Overall Survival

The nonparametric Kaplan-Meier method will be used to estimate the survival curves. Treatment differences in survival will be assessed by the stratified log-rank test (based on the stratification factors outlined 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) between the treatment arms. 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. Analysis using the RMST method may be used for OS to account for the possible nonproportional hazards effect.

Further details of sensitivity analyses will be described in the sSAP as needed.

9.6.1.3 Objective Response Rate and Duration of Response

The stratified Miettinen and Nurminen method will be used for comparison of ORR between treatment arms. The difference in ORR and its 95% CI from the stratified Miettinen and Nurminen method with strata weighting by sample size will be reported. The stratification factors used for randomization (Section 6.3.2) will be used in the analysis.

The point estimate of ORR will be provided by treatment group, together with 95% CI using exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934].

If sample size permits, DOR will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of participants who show a confirmed CR or PR will be included in this analysis.

For each DOR analysis, a corresponding summary of the reasons responding participants are censored will also be provided. Responding participants who are alive, have not progressed, have not initiated new anticancer therapy, and have not been determined to be lost to follow-up, and have had a disease assessment within ~5 months of the data cutoff date are considered ongoing responders at the time of analysis. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. Censoring rules for DOR are summarized in Table 13.

Table 13 Censoring Rules for Duration of Response

Situation	**Date of Progression or Censoring**	**Outcome**
No progression or death, no new anticancer therapy initiated	Last adequate disease assessment	Censor (Nonevent)
No progression or death, new anticancer therapy initiated	Last adequate disease assessment before new anticancer therapy initiated	Censor (Nonevent)
Death or progression immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Earlier date of last adequate disease assessment prior to ≥2 missed adequate disease assessments and new anticancer therapy, if any	Censor (Nonevent)
Death or progression after ≤1 missed disease assessment and before new anticancer therapy, if any	PD or death	End of response (Event)

Abbreviation: PD = progressive disease

Note: A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.

9.6.1.4 Analysis Strategy for Key Efficacy Endpoints

Table 14 summarizes the primary analysis strategy for key efficacy endpoints.

Table 14 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 12
OS	Testing: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at the date participants last known to be alive
Secondary Analyses:			
ORR (RECIST 1.1 by BICR)	Testing and Estimation: Stratified Miettinen and Nurminen method	ITT	Participants with missing data are considered nonresponders
DOR (RECIST 1.1 by BICR)	Descriptive statistics for range and Kaplan-Meier estimate of median	All responders in ITT	Censored according to the rules in Table 13
Abbreviations: BICR = blinded independent central review; DOR = duration of response; ITT = intention-to-treat; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1 Sensitivity analyses will be performed for PFS, ORR, and DOR based on investigator's assessment.			

9.6.2 Statistical Methods for Safety Analyses

Part 1: Participants will be closely followed for DLTs for 21 days after the first dose of study intervention. Descriptive summary statistics (eg, counts, percentages) will be provided for DLTs by treatment as appropriate.

Part 2: Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory test results, vital sign results, and ECG results.

The analysis of safety results will follow a tiered approach (Table 15). The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as system organ class terms) and events that meet predefined limits of change (PDLCs) in laboratory, vital sign, and ECG parameters are either prespecified as “Tier 1” events, or will be classified as belonging to “Tier 2” or “Tier 3” based on the number of events observed.

Tier 1 Events

Safety parameters or AEs of special interest that are identified a priori constitute "Tier 1" safety events that will be subject to inferential testing for statistical significance. There are no Tier 1 events for this protocol. 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. The combination of pembrolizumab and lenvatinib has not been associated with any new safety signals. Finally, there are no known AEs associated with participants with NSCLC for which determination of a p-value is expected to impact the safety assessment.

Tier 2 Events

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

Membership in Tier 2 requires that at least 10% of participants in any treatment arm exhibit the event. The threshold of at least 10% was chosen because participants enrolled in this study are in critical condition and usually experience various AEs of similar types regardless of treatment, events reported less frequently than in 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, Grades 3 to 5 AEs (≥5% of participants in one of the treatment arms) and SAEs (≥5% of participants in one of the treatment arms) will be considered Tier 2 events. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not a formal method for assessing the statistical significance of the between-treatment differences.

Tier 3 Events

Safety events that are not Tier 1 or Tier 2 events will be considered Tier 3 events. Only point estimates by treatment arm will be provided for Tier 3 safety parameters.

Continuous Safety Measures

For continuous measures such as changes from baseline in vital sign parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment arm in table format. For laboratory parameters, the number and percentage of participants with increases from baseline in laboratory test toxicity grades based on the highest postbaseline toxicity grade, and shift of toxicity grade from baseline to the worst postbaseline toxicity grade, will be summarized by treatment arm.

Table 15 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE (≥10% of participants in one of the treatment arms)	X	X
	Any Grades 3 to 5 AE (≥5% of participants in one of the treatment arms)	X	X
	Any serious AE (≥5% of participants in one of the treatment arms)	X	X
Tier 3	Any AE		X
	Any change from baseline results (laboratory tests, vital signs, ECGs)		X
Abbreviations: AE = adverse event, CI = confidence interval; ECG = electrocardiogram			

9.6.3 Statistical Methods for PRO Analyses

PRO analyses will be performed in Part 2 participants only.

Mean change from baseline

The time point for the mean change from baseline will be determined based on blinded data review prior to the database lock for any PRO analysis and documented in the sSAP.

To assess the treatment effects on the PRO score change from baseline in the PRO endpoints defined in Section 9.4.3, a cLDA model proposed by Liang and Zeger [Liang, K.-Y. and Zeger, S. L. 2000] will be applied, with the PRO score as the response variable, and treatment, time, the treatment by time interaction, and stratification factors used for randomization (See Section 6.3.2) as covariates. The treatment difference in terms of LS mean change from baseline will be estimated from this model together with 95% CI. Model-based LS mean with 95% CI will be provided by treatment group for PRO scores at baseline and postbaseline time point.

Time to True Deterioration (TTD)

For the TTD endpoints defined in Section 9.4.3, the Kaplan-Meier method will be used to estimate the TTD curve for each treatment group. The estimate of median TTD and its 95% CI will be obtained from the Kaplan-Meier estimates. The treatment difference in TTD will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling and with a single treatment covariate will be used to assess the magnitude of the treatment difference (ie, HR). The HR and its 95% CI will be reported. The same stratification factors used for the stratified PFS and OS analyses will be used as the stratification factors in both the stratified log-rank test and the stratified Cox model.

9.6.4 Summaries of Baseline Characteristics and Demographics

Part 1 and Part 2: The comparability of the treatment arms for each relevant demographic and baseline 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 screening failure and discontinuation will be displayed. Demographic variables (such as age), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

9.7.1 Interim Analysis for Part 1

In this open-label safety run-in phase, participants will be closely followed for DLTs for 21 days after the first dose of study intervention.

9.7.2 Interim Analysis for Part 2

Blinding to treatment assignment will be maintained at all investigational sites. The results of interim analyses will not be shared with the investigators prior to the completion of the study. Participant-level unblinding will be restricted to an external unblinded statistician and scientific programmer performing the interim analysis, who will have no other responsibilities associated with the study.

An external DMC 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 the Executive Oversight Committee. If the DMC recommends modifications to the design of the protocol or discontinuation of the study, this executive committee (and potentially other limited Sponsor personnel) may be unblinded to results at the treatment level in order 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 DMC Charter. Key aspects of the interim analyses are described in Section 9.7.2.2.

Treatment-level results from the interim analyses will be provided to the DMC by the unblinded statistician. 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.

9.7.2.1 Efficacy Interim Analyses

There are 3 planned IAs in addition to the FA for this study. For ORR efficacy IA1, the first ~420 randomized participants will be included. For subsequent IAs and the final efficacy analysis, all randomized participants will be included. Results of the IAs will be reviewed by the external DMC. Details of the boundaries for establishing statistical significance with regard to efficacy are discussed further in Section 9.8.

The analyses planned, endpoints evaluated, and drivers of timing are summarized in Table 16. OS will only be examined at IA1 if the external DMC suggests it is necessary to evaluate risk benefit for any safety considerations. There is no intent to declare a positive finding for OS at IA1. The HR lower bound will be calculated using asymmetric nonbinding testing with Pocock spending function under the alternative hypothesis. The probability of crossing the lower bound HR of 1.2814 is approximately 0.1% if the underlying HR is 0.725.

Table 16 Summary of Interim and Final Analyses Strategy

Analysis	Key Endpoint(s)	Timing	Estimated Time after First Participant Randomized	Primary Purpose of Analysis
IA1	ORR	~ 420 participants randomized with ~ 9 months of follow-up	~ 19 months	Final ORR analysis
IA2	PFS; OS	Both ~ 420 PFS events have occurred and ~ 8 months after last participant randomized	~ 26 months	Interim PFS analysis Interim OS analysis
IA3	PFS; OS	Both ~ 480 PFS events have occurred and ~18 months after last participant randomized	~ 36 months	Final PFS analysis Interim OS analysis
FA	OS	Both ~ 445 deaths have occurred and ~ 29 months after last participant randomized	~ 47 months	Final OS analysis

Note that for IA2, IA3 and the FA, if the events accrue slower than expected, the Sponsor may conduct the analysis with additional 2 months of follow-up, or the specified number of events is observed, whichever occurs first.

Abbreviations: FA = final analysis; IA = interim analysis; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

9.7.2.2 Safety Interim Analyses

In Part 2, an external DMC will review accumulating safety data periodically. The first safety data review will occur after at least 40 participants (~ 10 participants treated with carboplatin in each treatment arm and ~ 10 participants treated with cisplatin in each treatment arm) complete at least 2 cycles of treatment to assess the safety and tolerability of lenvatinib when administered in combination with platinum doublet chemotherapy and pembrolizumab. Further details of the timing of safety monitoring will be specified in the DMC Charter.

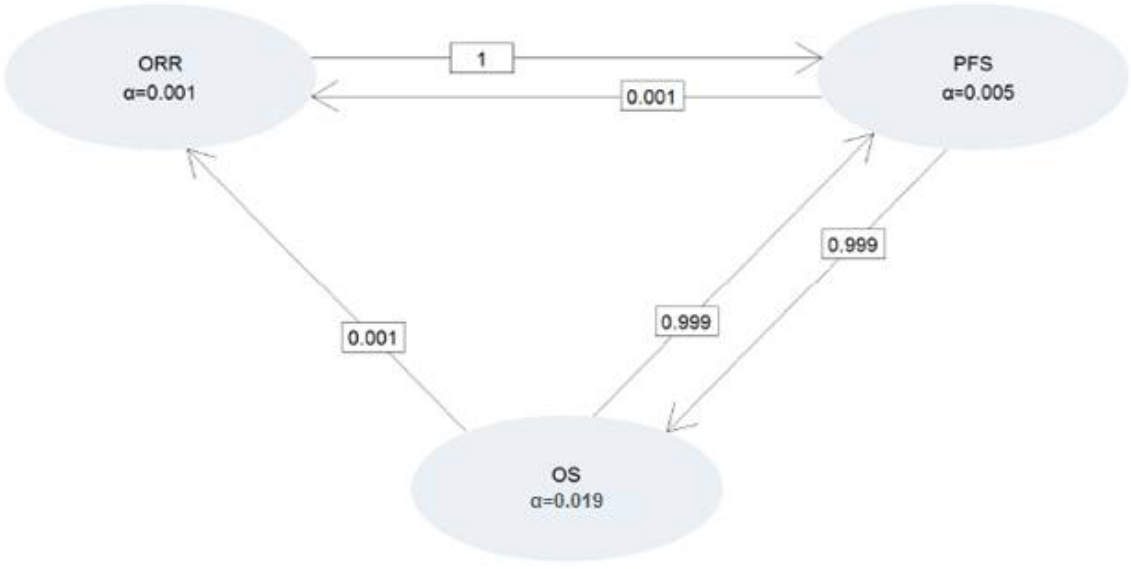
9.8 Multiplicity

9.8.1 Multiplicity for Part 1

No multiplicity adjustment is planned.

9.8.2 Multiplicity for Part 2

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 IAs. According to this approach, study hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the alpha allocated to that hypothesis can be reallocated to other hypothesis tests. Figure 3 shows the initial one-sided alpha allocation for each hypothesis in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses.



Abbreviations: α = alpha; IA = interim analysis; ORR = objective response rate; OS = overall survival; PFS = progression-free survival

Note: If both PFS and OS null hypotheses are rejected, the reallocation strategy allows re-testing of ORR at alpha = 0.025 based on the ORR p-value at IA1.

Figure 3 Type I Error Reallocation Strategy Following Closed Testing Principle

9.8.2.1 Objective Response Rate

The study will test ORR only once at IA1, at an initial alpha level of 0.001 (Figure 3). Note that if superiority for both the PFS and OS hypotheses is declared at a future planned analysis, $\alpha = 0.024$ will be rolled over to the hypothesis for ORR, then the test statistics previously computed at IA1 for the ORR hypothesis will be used for inferential testing with an updated alpha level of 0.025.

Based on the first 420 randomized participants with at least 9 months of follow-up, power at the initially assigned alpha level and the maximum possible alpha level as well as the approximate treatment difference required to reach the bound (ΔORR) are shown in Table 17, assuming underlying 48% and 68% response rates in the control and experimental groups, respectively.

Table 17 Possible Alpha-levels and Approximate ORR Difference Required to Demonstrate Efficacy for ORR at IA1

Alpha	**~Δ Objective Response Rate (ORR)**	**Power (Δ ORR = 0.2)**
0.001	~ 0.15	83%
0.025	~ 0.10	98%
Abbreviations: IA = interim analysis; ORR = objective response rate		

9.8.2.2 Progression-free Survival

The study will test PFS at IA2 and IA3 only. Following the multiplicity strategy as outlined in Figure 3, the PFS hypothesis may be tested at α=0.005 (initially allocated alpha), at α=0.006 (if the ORR null hypothesis is rejected but not the OS hypothesis), at α=0.023981 (if the OS null hypothesis is rejected but not the ORR hypothesis), or at α=0.025 (if both the OS and ORR null hypotheses are rejected). For the superiority hypothesis, a Lan-DeMets alpha-spending function approximating O'Brien-Fleming bounds is used to construct group sequential boundaries to control the Type I error rate. Table 18 shows the boundary properties for each of these alpha levels for the PFS analysis. Note that the final row indicates the total power to reject the null hypothesis for PFS at each alpha level. Also, note that if the OS null hypothesis is rejected at IA3 or FA of the study, the previously computed PFS test statistics may be used for inferential testing with its updated bounds, considering the alpha reallocation from the OS hypothesis.

Table 18 Efficacy Boundaries and Properties for Progression-free Survival Analyses

Analysis	Value	α = 0.005	α = 0.006	α =0.023981	α = 0.025
IA 2: 88%[1] N: 714 Events: ~ 420 Month: 26	Z	2.7831	2.7155	2.1492	2.1304
	p (1-sided)[2]	0.0027	0.0033	0.0158	0.0166
	HR at bound[3]	0.762	0.767	0.8106	0.8121
	P (Cross) if HR = 1[4]	0.0027	0.0033	0.0158	0.0166
	P (Cross) if HR = 0.7[5]	0.8094	0.827	0.9337	0.9361
IA 3 N: 714 Events: ~ 480 Month: 36	Z	2.6344	2.5732	2.063	2.0462
	p (1-sided)[2]	0.0042	0.005	0.0196	0.0204
	HR at bound[3]	0.7861	0.7905	0.8282	0.8295
	P (Cross) if HR = 1[4]	0.005	0.006	0.024	0.025
	P (Cross) if HR = 0.7[5]	0.9045	0.9146	0.9705	0.9717

Abbreviations: α = alpha; FA = final analysis; HR = hazard ratio; IA = interim analysis; N = number

1. Percentage of total planned events at the interim analysis.
2. p (1-sided) is the nominal alpha for group sequential testing.
3. HR at bound is the approximate HR required to reach an efficacy bound.
4. P (Cross if HR = 1) is the probability of crossing a bound under the null hypothesis.
5. P (Cross if HR = 0.7) is the probability of crossing a bound under the alternative hypothesis.

Note: Number of events and timing of analyses are estimated.

9.8.2.3 Overall Survival

The study will test OS at IA2, IA3 and FA. Following the multiplicity strategy as outlined in Figure 3, the OS hypothesis may be tested at α=0.019 (initially allocated alpha), or α=0.023995 (if the PFS null hypothesis is rejected but not the ORR hypothesis), or α=0.025 (if both the PFS and ORR null hypotheses are rejected). Table 19 shows the bounds and boundary properties for OS hypothesis testing derived using a Lan-DeMets spending function approximating O'Brien-Fleming bounds.

Table 19 Efficacy Boundaries and Properties for Overall Survival Analyses

Analysis	**Value**	**α = 0.019**	**α = 0.023995**	**α = 0.025**
IA 2: 59%[1] N: 714 Events: ~ 264 Month: 26	Z	2.8338	2.7114	2.6895
	p (1-sided)[2]	0.0023	0.0033	0.0036
	HR at bound[3]	0.7051	0.7159	0.7178
	P (Cross) if HR = 1[4]	0.0023	0.0033	0.0036
	P (Cross) if HR = 0.725[5]	0.4113	0.4594	0.4679
IA 3: 82%[1] N: 714 Events: ~ 364 Month: 36	Z	2.3744	2.2723	2.254
	p (1-sided)[2]	0.0088	0.0115	0.0121
	HR at bound[3]	0.7795	0.788	0.7895
	P (Cross) if HR = 1[4]	0.0095	0.0126	0.0132
	P (Cross) if HR = 0.725[5]	0.7601	0.7911	0.7963
FA N: 714 Events: ~ 445 Month: 47	Z	2.1436	2.0524	2.0360
	p (1-sided)[2]	0.0160	0.0201	0.0209
	HR at bound[3]	0.8160	0.8231	0.8244
	P (Cross) if HR = 1[4]	0.0190	0.0240	0.0250
	P (Cross) if HR = 0.725[5]	0.9000	0.9155	0.9180

Abbreviations: α = alpha; FA = final analysis; HR = hazard ratio; IA = interim analysis; N = number

1. Percentage of total planned events at the interim analysis.
2. p (1-sided) is the nominal alpha for group sequential testing.
3. HR at bound is the approximate HR required to reach an efficacy bound.
4. P (Cross if HR = 1) is the probability of crossing a bound under the null hypothesis.
5. P (Cross if HR = 0.725) is the probability of crossing a bound under the alternative hypothesis.

Note: Number of events and timing of analyses are estimated.

The bounds provided in Table 18 and Table 19 above are based on the assumption that the expected number of PFS events at IA2 and IA3 (FA for PFS) are 420 and 480, respectively, and number of OS events at IA2, IA3 and FA are 264, 364, and 445, respectively. At the time of an analysis, the observed number of events may differ substantially from the expected. To avoid overspending at an IA and leave reasonable alpha for the FA, the minimum alpha-spending strategy will be adopted. At an IA, the information fraction used in Lan-DeMets spending function to determine the alpha-spending at the IA will be based on the minimum of the expected information fraction and the actual information fraction at each analysis. Specifically,

- In the scenario that the events accrue slower than expected and the observed number of events is less than the expected number of events at a given analysis, the information

fraction will be calculated as the observed number of events at the IA over the target number of events at FA.

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

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

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

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

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Efficacy Analyses

Part 1

Approximately 12 participants will be enrolled in Part 1. The total sample size is based on clinical considerations and not statistical considerations.

Part 2

The study will randomize ~714 participants in a 1:1 ratio into each arm. PFS and OS are primary endpoints for the study, with ORR and DOR as the secondary endpoints.

With ~ 420 participants with at least 9 months of follow-up, the study has ~ 83% power to detect a 20% point difference in ORR between an underlying 48% ORR in the control arm and a 68% ORR in the experimental arm at an initially assigned 0.001 (one-sided) significance level.

For the PFS endpoint, based on a target number of ~ 480 events at the final PFS analysis and 1 IA at approximately 88% of the target number of events, the study has approximately 90% power to detect a HR of 0.7 at an initially assigned 0.005 (one-sided) significance level.

For the OS endpoint, based on a target number of ~ 445 events and 2 IAs at approximately 59% and 82% of the target number of events, the study has approximately 90% power to detect a HR of 0.725 at an initially assigned 0.019 (-one-sided) significance level.

Based on KEYNOTE-189 data, the above sample size and power calculations for PFS and OS assume the following:

- PFS follows a piecewise exponential distribution, with the first piece median as 8.8 months and monthly hazard rate as 0.08 up to 15 months, and second piece median as 17 months and monthly hazard rate as 0.04 for the control group
- OS follows an exponential distribution, with a median of 22 months for the control group
- Enrollment period is approximately 18 months
- Annual drop-out rate is 15% and 2% for PFS and OS, respectively
- Follow-up period is approximately 18 and 29 months for PFS and OS, respectively, after the last participant is randomized

The sample size and power calculations were performed in R (package “gsDesign”).

Extension Study in China

To evaluate the consistency of efficacy and safety in the population in China compared with the global population, after completion of global study enrollment, participants in China will continue to be randomized in a 1:1 ratio into the lenvatinib + pembrolizumab + platinum doublet chemotherapy arm and the matching placebo + pembrolizumab + platinum doublet chemotherapy arm until the planned sample size of approximately 200 participants in China is reached. Participants in China randomized after completion of enrollment in the global study will not be included in the analysis of the global study.

9.10 Subgroup Analyses

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

- Stratification factors
  - PD-L1 TPS (<50% vs. ≥50%)
  - Geographic site (East Asian vs. non-East Asian)

    - ECOG performance status at Screening (0 vs. 1)

- PD-L1 TPS (<1%, 1% to 49%, ≥50%)
- PD-L1 TPS (<1%, ≥1%)
- Age category (<65 years, ≥65 years)
- Sex (female, male)
- Race (white, nonwhite)
- Brain metastasis (presence vs. absence at Screening)
- Liver metastasis (presence vs. absence at Screening)
- Smoking status (never vs. former/current smoker)
- Investigator's choice of chemotherapy

The consistency of the treatment effect will be assessed using descriptive statistics for each category of the subgroup variables listed above. If the number of participants in a category of a subgroup variable is <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. Unless further specified in the sSAP, the subgroup analyses for PFS and OS will be conducted using an unstratified Cox model, and the subgroup analyses for ORR will be conducted using the unstratified Miettinen and Nurminen method.

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.

9.12 Extent of Exposure

The extent of exposure for a participant is defined as the number of cycles in which the participant received study intervention. 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 and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials 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 (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. 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 (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and 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 potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

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

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

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

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

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, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), 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 and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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 Steering Committee

This study will be conducted in consultation with a Steering Committee. The Steering Committee is composed of:

- Sponsor personnel;
- Eisai personnel;
- Investigators participating in the study; and
- Consulting therapeutic area and clinical study experts.

The Steering Committee will provide guidance on the operational aspects of the study, provide input with respect to study design, interpretation of results and subsequent peer-reviewed scientific publications.

Specific details regarding responsibilities and governance of the Steering Committee will be described in a separate charter.

10.1.4.2 Executive Oversight Committee

The Executive Oversight Committee (EOC) is comprised of members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the DMC or Steering Committee 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 OR external collaborating organization 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 participants' documented informed consent, 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 20 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study if determined necessary by the investigator or required by local regulations.
- 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 subject's participation in the study.

Table 20 Protocol-required Safety Laboratory Assessments

Hematology	Comprehensive Chemistry Panel	Urinalysis	Other
Hematocrit Hemoglobin Platelet count RBC WBC count with differential (absolute or percentage): Neutrophils Lymphocytes Monocytes Eosinophils Basophils	Albumin Alkaline phosphatase ALT AST Carbon dioxide (CO_2 or Bicarbonate)[a] Calcium Chloride Creatinine Glucose Magnesium Phosphorus Potassium Sodium Total bilirubin Direct bilirubin, if total bilirubin is elevated above the upper limit of normal Total protein BUN or Urea[b] Amylase Lipase	Blood Glucose Protein Specific gravity Microscopic examination, if abnormal results are noted	Follicle-stimulating hormone (FSH)[c] Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test[d] Hepatitis B and C testing[e,f] HIV testing[f] PT/INR and aPTT/PTT Total T3, FT4, and TSH[g,h] Plasma sample for lenvatinib PK Serum for pembrolizumab PK Antipembrolizumab antibodies Blood sample for carboplatin PK Blood sample for cisplatin PK Blood sample for pemetrexed PK Blood for genetic analysis Blood for serum biomarkers Blood for RNA analysis Blood for circulating tumor nucleic acids Blood for plasma biomarkers

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; DNA = deoxyribonucleic acid; FT3 = free triiodothyronine; FT4 = free thyroxine; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; PK = pharmacokinetics; PT = prothrombin time; PTT = partial thromboplastin time; RNA = ribonucleic acid; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WBC = white blood cell; WOCBP = women of childbearing potential

[a] Carbon dioxide or bicarbonate, only if available as standard of care in the region

[b] BUN or urea (one or the other should be collected per institutional standard).

[c] If necessary, to check menopausal status.

[d] Perform on WOCBP only 24 hours before first dose. Pregnancy tests must be repeated before every cycle.

[e] HBsAg or HBV-DNA. HCV-RNA (qualitative) or HCV antibody.

[f] Not required unless mandated by local health authorities.

[g] After Cycle 1, participants may be dosed while thyroid function test results are pending.

[h] Free T3/T4 is acceptable when total T3/T4 cannot be determined.

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 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."

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.

10.3.2 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.

10.3.3 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

10.3.4 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 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.

10.3.5 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

This section is 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 following 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, Mullerian 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 follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 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 of childbearing potential are eligible to participate if they agree to consistently and correctly use of a highly effective method of contraception as described in Table 21 during the protocol defined- time frame in Section 5.1.

Table 21 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] Intrauterine hormone-releasing system (IUS)[c] Intrauterine device (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 Clinical Trial Facilitation Group (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 lactational amenorrhea method (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).

In addition, during treatment and up to 180 days after the last dose of treatment with chemotherapeutic agents, female participants must also agree not to donate eggs (ova, oocytes) to others or freeze/store eggs for their own use for the purpose of reproduction.

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 of the first dose of study intervention. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study in the event of a positive test result. Repeated pregnancy test (such as monthly testing) may be conducted if required by local regulation. WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

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

10.6 Appendix 6: Description of the iRECIST Process for Assessment of Disease Progression

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 to guide decisions about changes in management.

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic PD 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 scans are obtained (using iRECIST for participant management [see Table 10 and Figure 2]).

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 by 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 Scans

On the confirmatory scans, 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 to any prior iUPD time point
    - For nontarget lesions, worsening is any significant growth in lesions overall, compared to 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 scans for confirmation are to be scheduled 4 to 8 weeks from the scans on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation scan 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 pseudo-progression, 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 Following the Confirmatory Scan

If repeat scans do not confirm PD and the participant continues to be clinically stable, study intervention is to continue. The regular scan schedule is to be followed. If PD is confirmed, participants may be discontinued from study intervention.

NOTE: If a participant has confirmed radiographic progression (iCPD) and clinically meaningful benefit, study intervention may be considered following consultation with the Sponsor. In this case, if study intervention is continued, tumor scans are to be performed following the intervals outlined in the SoA (Section 1.3).

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (ie, after iSD/iPR/iCR), another instance of progression (another 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 pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire study, either before or after an instance of pseudo-progression.
- 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 on the subsequent iUPD is identical to the iUPD confirmation process for the initial PD, with one exception, which can occur if new lesions had occurred at a prior instance of iUPD, had not resolved, then worsened (increase in size or number) leading to the second iUPD. If new lesion worsening has not resolved at the confirmatory scan, 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 new or worsening causes of progression indicates iCPD.

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

10.7 Appendix 7: Country-specific Requirements

10.7.1 Germany-specific Requirements

1. Exclusion Criterion 8: HIV testing is mandatory.

2. Exclusion Criterion 9: Hepatitis B and C testing is mandatory.

3. Exclusion Criterion 13: TB testing is mandatory.

4. Section 8.4.1 (Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information): All AEs meeting serious criteria are to be collected for 120 days after the last dose of study intervention.

5. Additional pregnancy tests at monthly intervals up to 120 days after the last dose of Pembrolizumab and/or Lenvatinib/Placebo and up to 180 days after the last dose of chemotherapeutic agents should also be performed if the participant initiates new anticancer therapy in that timeframe.

10.7.2 UK-specific Requirements

1. Section 6.5.2, Prohibited Concomitant Medications: Live vaccines must not be administered for 90 days after the last dose of study intervention.

2. In extenuating circumstances only, when a central supply of pembrolizumab is not readily available, pembrolizumab may be sourced locally after consultation with and approval by the Sponsor.

10.7.3 Japan-specific Requirements

1. For the assistance to early diagnosis of pneumonitis/ILD in study participants, the following items such as pulse oximetry monitoring (SpO_2), CRP, KL-6, and SP-D will be measured in this study. These items should be measured in the following timing.

    - SpO_2: at the timing of vital sign assessment.

    - CRP, KL-6 and SP-D: at Screening*, predose of Day 1 of every cycle, end of treatment and Safety Follow-up Visit (30 days after last dose).

        1. * Should be measured at the timing of clinical laboratory tests (such as hematology/ chemistry).

2. In the case that pneumonitis/ILD occurs regardless of causality with study medication, an independent ILD evaluation committee will conduct adjudication of cases of the pneumonitis/ILD. For this purpose, relevant data such as chest imaging (from the baseline to the recovery of pneumonitis/ILD) will be submitted to MSD K.K.

10.7.4 Argentina-specific Requirements

1. Exclusion Criterion 8: HIV testing is mandatory

2. Exclusion Criterion 9: Hepatitis B and C testing is mandatory

10.7.5 France-specific Requirements

Treatment with pembrolizumab should be permanently discontinued in cases of confirmed Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).

10.7.6 Canada-specific Requirements

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

2. 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.

3. Section 6.6.2.1 - Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab:
   Pembrolizumab should be permanently discontinued in case of confirmed TEN or SJS.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
ADA	Antidrug antibody
ADL	Activities of daily living
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
ALT	Alanine transaminase
APaT	All Participants as Treated
ASCO	American Society of Clinical Oncology
AST	Aspartate transaminase
AUC	Area under the plasma drug concentration time curve
BICR	Blinded independent central review
BP	Blood pressure
CI	Confidence interval
cLDA	Constrained longitudinal data analysis
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CRF	Case Report Form
CRP	C-reactive protein
CSF	Colony-stimulating factor
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CVA	Cerebrovascular accident
CYP	Cytochrome P450
DILI	Drug-induced liver injury
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DOR	Duration of response
DTC	Differentiated thyroid cancer
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form

Abbreviation	Expanded Term
EGFR	Epidermal growth factor receptor
EDC	Electronic data collection
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC	European Organisation for Research and Treatment of Cancer
EQ	EuroQoL
FA	Final analysis
FAS	Full Analysis Set
FDA	US Food and Drug Administration
FFPE	Formalin fixed, paraffin-embedded
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health related quality of life
HRT	Hormone replacement therapy
IA	Interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCPD	iRECIST-confirmed radiographic progression
iCR	iRECIST complete response
iCRO	imaging Contract Research Organization
IEC	Independent Ethics Committee
IgG4	Immunoglobulin G4
IHC	Immunohistochemistry
ILD	interstitial lung disease
IND	Investigational New Drug
iPR	iRECIST partial response
irAE	Immune-related AEs
IRB	Institutional Review Board

Abbreviation	Expanded Term
iRECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1 for immune-based therapeutics
iSD	iRECIST stable disease
ITT	Intent-to-treat
IUD	Intrauterine device
iUPD	iRECIST-unconfirmed progressive disease
IUS	Intrauterine hormone-releasing system
IV	Intravenous
1L	Front-line (or first-line)
KL-6	Krebs von den Lungen-6 antigen
LMWH	Low molecular-weight heparin
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody
MASCC	Multinational Association of Supportive Care in Cancer
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
mRNA	messenger RNA
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ONJ	Osteonecrosis of the jaw
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD 1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PDGFRα	Platelet-derived growth factor receptor-alpha
PFS	Progression-free survival
Pgp	P glycoprotein
PK	Pharmacokinetic
PR	Partial response
PRES	Posterior reversible encephalopathy syndrome
PRO	Patient-reported outcome
PS	Performance status
qd	Once daily

Abbreviation	Expanded Term
QoL	Quality of life
QLQ	Quality of Life Questionnaire
QLQ-LC13	Quality of Life Questionnaire and Lung Cancer Module 13
QLQ-C30	Quality of Life Questionnaire Core 30
Q3W	Every 3 weeks
RCC	Renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
ROS1	ROS proto-oncogene 1
RPLS	Reversible posterior leukoencephalopathy syndrome
RTKi	Receptor tyrosine kinase inhibitor
SAE	Serious adverse event
SD	Stable disease
SJS	Stevens-Johnson syndrome
SoA	Schedule of Activities
SOC	Standard of care
SP-D	Surfactant protein D
SpO_2	blood oxygen saturation
sSAP	Supplemental statistical analysis plan
TAM	Tumor-associated macrophage
TEN	Toxic epidermal necrolysis
TPS	Tumor proportion score
TTD	Time to true deterioration
UPCR	Spot urine protein-to-creatinine ratio
VAS	Visual analog scale
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WOCBP	Woman/women of childbearing potential
WONCBP	Woman/women of nonchildbearing potential

10.9 Appendix 9: MASCC 2016 Guidelines

DEXAMETHASONE		Dose and Schedule
High Risk	- Acute Emesis	20 mg once (12 mg when used with (fos)aprepitant or netupitant)**
	- Delayed Emesis	8 mg bid for 3 - 4 days (8 mg once daily when used with (fos)aprepitant or netupitant)
Moderate Risk	- Acute Emesis	8 mg once
	- Delayed Emesis	8 mg daily for 2 - 3 days (many panelists give the dose as 4 mg bid)
Low Risk	- Acute Emesis	4 - 8 mg once

* While corticosteroids other than dexamethasone are effective antiemetics, the dose and schedule of dexamethasone coupled with its wide availability in various dose forms established it as the guideline agent of choice.

** The 12 mg dose of dexamethasone is the only one tested with (fos)aprepitant/netupitant in large randomized trials.

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http://www.mascc.org/antiemetic-guidelines

Investigators may use local equivalent or more current guidelines, if available.

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