Official Protocol Title:	A Phase 3, multicenter, randomized, open-label trial to compare the efficacy and safety of pembrolizumab (MK-3475) in combination with lenvatinib (E7080/MK-7902) versus docetaxel in previously treated participants with metastatic non-small cell lung cancer (NSCLC) and progressive disease (PD) after platinum doublet chemotherapy and immunotherapy (LEAP-008)
NCT number:	NCT03976375
Document Date:	08-December-2023

TITLE PAGE

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Protocol Title: A Phase 3, multicenter, randomized, open-label trial to compare the efficacy and safety of pembrolizumab (MK-3475) in combination with lenvatinib (E7080/MK-7902) versus docetaxel in previously treated participants with metastatic non-small cell lung cancer (NSCLC) and progressive disease (PD) after platinum doublet chemotherapy and immunotherapy (LEAP-008)

Protocol Number: 008-09 (E7080-G000-316)

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

Sponsor Name: Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

The study is co-funded by MSD and Eisai.

Legal Registered Address:

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

NCT	Not Applicable
EU CT	2022-501439-18-00
EudraCT	2018-003791-12
JRCT	Not Applicable
WHO	Not Applicable
UTN	Not Applicable
IND	140221

Approval Date: 08 December 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
Amendment 9	08-DEC-2023	The study is to be discontinued based on the observation that the combination of pembrolizumab + lenvatinib versus docetaxel monotherapy 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 IA2.
Amendment 8	27-FEB-2023	Updated to align with the Protocol Clarification Letter, which specified to follow the more stringent contraception requirements for male and female participants if included in local label for specific country.
Amendment 7	12-AUG-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. Additional changes were made throughout the protocol to align with the EU CTR.
Amendment 6	28-APR-2021	To update the dose modification and toxicity management guidelines for irAEs. The protocol was amended to update the CTCAE version within Dose Modification and Toxicity Management Guidelines for irAEs and table that was used in this study.
Amendment 5	26-MAR-2021	To provide guidance regarding osteonecrosis of the jaw for participants treated with lenvatinib; alignment with lenvatinib program standards, revised informed consent language in response to COVID-19 for in-person visit safety considerations to allow documented (oral) consent if allowable by IRB/IEC and local Health Authority; updated pembrolizumab dose modification table.

Document	Date of Issue	Overall Rationale
Amendment 4	27-MAY-2020	Amended to clarify and update futility analyses criteria, to align Section 9.1 and Section 9.7.2 of the SAP, to adjust DCR12 evaluation requirements, to provide additional guidance to investigators regarding dose modifications and overdose reporting, to include lenvatinib label safety updates, and to include country-specific requirements for enrollment.
Amendment 3	16-JAN-2020	Progressive disease (PD) during/after platinum doublet chemotherapy is for treatment of metastatic disease, therefore a clarification was added to the platinum doublet chemotherapy (inclusion criterion #3). The clarification states that completion of treatment with a platinum doublet chemotherapy as neoadjuvant, adjuvant, or definitive chemo-radiation treatment for early stage disease (Stage I-III) within 1 year of signing the ICF will satisfy the prior platinum doublet chemotherapy treatment requirement. In addition, an update was added to the immunotherapy refractory criteria (inclusion criterion #2), treatment with only one prior anti-PD-1/PD-L1 immunotherapy is permitted.
Amendment 2	28-AUG-2019	Removal of the second confirmatory image for PD; added MUGA/ECHO at baseline for all participants; significant updates to the Inclusion and Exclusion Criteria; general template updates.
Amendment 1	04-APR-2019	Amended to update the study design.
Original Protocol	18-DEC-2018	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 09

Overall Rationale for the Amendment:

The study is to be discontinued based on the observation that the combination of pembrolizumab + lenvatinib versus docetaxel monotherapy 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 IA2.

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 docetaxel monotherapy. Upon study termination, participants are discontinued and may be enrolled in an extension study, if available.	This change addresses new data that recently became available. The combination of pembrolizumab + lenvatinib versus docetaxel monotherapy 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 IA2.
Other Changes in Amendment		
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 Number and Name	Description of Change	Brief Rationale
Section 1.1, Synopsis	Table: Intervention Groups and Duration: To 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 docetaxel monotherapy. Upon study termination, participants are discontinued and may be enrolled in an extension study, if available.	Refer to Section 1.1 rationale.
Section 4.4, Beginning and End-of-Study Definition	Participants may be enrolled in an extension study upon discontinuation at study termination.	Refer to Section 1.1 rationale.
Section 6.1, Study Intervention(s) Administered	Note on study-specific investigator letter has been added regarding participants still receiving study treatment.	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 8.2.1.4, 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 Number and Name	Description of Change	Brief Rationale
Section 8.8, Biomarkers	Sample collection will be discontinued.	Refer to Section 1.1 rationale.
Section 8.10.3, Second Course Treatment	Treatment of participants with study interventions is clarified. Note on study-specific investigator letter has been added.	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, multicenter, randomized, open-label trial to compare the efficacy and safety of pembrolizumab (MK-3475) in combination with lenvatinib (E7080/MK-7902) versus docetaxel in previously treated participants with metastatic non-small cell lung cancer (NSCLC) and progressive disease (PD) after platinum doublet chemotherapy and immunotherapy (LEAP-008)

Short Title: Pembrolizumab with Lenvatinib versus Docetaxel for Metastatic NSCLC after Platinum Doublet Chemotherapy and Immunotherapy

Acronym: Protocol 008

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In participants with metastatic NSCLC and PD after platinum doublet chemotherapy and treatment with 1 prior anti-PD-1/PD-L1 monoclonal antibody (mAb):

Note: Progression-free survival (PFS), objective response rate (ORR), duration of response (DOR), and disease control rate at 12 weeks (DCR12) will be assessed per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

Note: Based on the data from the final safety and efficacy analysis for LEAP-008 (data cutoff 11-AUG-2023), the combination of pembrolizumab + lenvatinib versus docetaxel monotherapy did not meet the prespecified criteria for the primary endpoint of overall survival (OS) at the final analysis and the second dual primary endpoint of PFS at IA2. Safety analysis will be performed at the end of the study; there will be no further analyses for efficacy and electronic patient-reported outcome endpoints.

Note: In alignment with the study-specific investigator letter dated 22-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 or docetaxel 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 09, participants who are still on study treatment will no longer require tumor response assessments by blinded independent central review (BICR) to be performed. Scans will no longer be submitted to the imaging Contract Research Organization. Participants who are still on study medication should continue tumor imaging assessment as assessed by investigator per protocol. Biomarker and pharmacokinetic specimen collection is discontinued.

Primary Objective	**Primary Endpoint**
To compare pembrolizumab + lenvatinib to docetaxel with respect to overall survival (OS). Hypothesis (H1): Pembrolizumab + lenvatinib prolongs OS compared with docetaxel.	OS, defined as the time from randomization to the date of death due to any cause.
To compare pembrolizumab + lenvatinib to docetaxel with respect to PFS per RECIST 1.1 by blinded independent central review (BICR). Hypothesis (H2): Pembrolizumab + lenvatinib prolongs PFS per RECIST 1.1 based on BICR compared with docetaxel.	PFS, defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurs first.
Secondary Objectives	**Secondary Endpoints**
To compare pembrolizumab + lenvatinib to docetaxel with respect to ORR per RECIST 1.1 by BICR. Hypothesis (H3): Pembrolizumab + lenvatinib results in a superior ORR per RECIST 1.1 based on BICR compared with docetaxel.	Objective response, defined as a confirmed complete response (CR) or partial response (PR).
To compare pembrolizumab + lenvatinib to lenvatinib monotherapy with respect to ORR per RECIST 1.1 by BICR. Hypothesis (H4): Pembrolizumab + lenvatinib results in a superior ORR per RECIST 1.1 based on BICR, compared with lenvatinib monotherapy.	Objective response, defined as a confirmed complete response (CR) or partial response (PR).
To assess DOR with pembrolizumab + lenvatinib and docetaxel per RECIST 1.1 by BICR.	DOR, defined as the time from the first documented evidence of CR or PR until PD or death due to any cause, whichever occurs first, in participants demonstrating CR or PR.
To assess the safety and tolerability of treatment with pembrolizumab + lenvatinib versus docetaxel. To assess the safety and tolerability of treatment with lenvatinib monotherapy.	Adverse events (AEs) and discontinuations due to AEs.

To compare pembrolizumab + lenvatinib to docetaxel with respect to the mean change from baseline in global health status/quality of life (QoL), cough, chest pain, dyspnea, and physical functioning.	Scores for the following scales/items: Global health status/QoL (European Organization for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire Core 30 items [QLQ-C30] Items 29 and 30) Cough (EORTC Quality of Life Questionnaire Lung Cancer Module 13 [QLQ-LC13] Item 31) Chest pain (EORTC QLQ-LC13 Item 40) Dyspnea (EORTC QLQ-C30 Item 8) Physical functioning (EORTC QLQ-C30 Items 1 to 5)
To compare pembrolizumab + lenvatinib to docetaxel with respect to time to true deterioration (TTD) in global health status/QoL, cough, chest pain, dyspnea, and physical functioning scales.	TTD, defined as the time from baseline to the first onset of ≥10-point decrease from baseline, with confirmation by the subsequent visit of ≥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) Physical functioning (EORTC QLQ-C30 Items 1 to 5)

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	The treatment of metastatic Non-small cell lung cancer with squamous or nonsquamous histology
Population	Participants with metastatic NSCLC who have experienced PD after platinum doublet chemotherapy and immunotherapy (in combination or sequentially), without restriction regarding PD-L1 expression.
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	Active Control Without Placebo
Study Blinding	Unblinded open-label
Blinding Roles	No blinding
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.

Number of Participants:

Approximately 405 participants will be randomized 4:4:1 to receive pembrolizumab + lenvatinib, docetaxel, or lenvatinib monotherapy. All participants will meet the study inclusion/exclusion criteria, follow the Schedule of Activities (SoA), and undergo safety monitoring as defined in the protocol.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Arm 1	Pembrolizumab	25 mg/mL	200 mg	IV Infusion	Q3W	Test Product
Arm 1	Lenvatinib	10 mg 4 mg	20 mg	Oral	QD	Test Product
Arm 2	Docetaxel	20 mg/ mL	75 mg/m^2	IV Infusion	Q3W	Comparator
Arm 3	Lenvatinib	10 mg 4 mg	24 mg	Oral	QD	Test Product

Abbreviations: IV = intravenous; PO = oral; Q3W = every 3 weeks; QD = once daily.

Total Number of Intervention Groups/Arms	3 arms
Duration of Participation	Each participant will be in the study from the time the participant provides documented informed consent through the final contact. The site's study team must have reviewed and submitted images that are of diagnostic quality from at least 2 dates: 1) imaging prior to anti-PD-1/PD-L1 treatment or an image showing nadir during anti-PD-1/PD-L1 treatment; AND 2) imaging to determine that radiographic progression has occurred per RECIST 1.1 within 12 weeks from the last dose of an anti-PD-1/PD-L1 mAb. These images will be submitted to the central imaging vendor (CIV) before randomization to confirm that the images are of diagnostic quality. The central vendor will not be confirming eligibility before randomization (see Section 8.2.1.1). Both archival tissue and tissue from a newly obtained biopsy will be submitted to the central vendor before randomization. The archival tissue for PD-L1 biomarker analysis will be used for stratification. Participants will provide tissue for analysis from a newly obtained formalin-fixed sample from a recent biopsy of a tumor lesion not previously irradiated, and without systemic antineoplastic therapy between the new biopsy and initiation of study intervention (ie, study drug or study treatment). **Note:** For participants from whom obtaining a new tumor biopsy will be medically inappropriate, the investigator may request an exception from the Sponsor's study clinical director. The request including details of why the biopsy is medically inappropriate will be documented in a Sponsor Consultation Form.

	After a screening phase of up to 42 days, participants will be randomly assigned to receive pembrolizumab + lenvatinib (Arm 1), docetaxel (Arm 2), or lenvatinib monotherapy (Arm 3). Each eligible participant will receive a randomization number. This will occur centrally using an interactive response technology (IRT) system. **Initial Treatment** **Pembrolizumab:** Participants may continue receiving pembrolizumab for up to 35 treatment cycles (~2 years), until PD or until a discontinuation criterion is met. **Lenvatinib:** Participants may continue receiving lenvatinib until PD or until a discontinuation criterion is met. **Docetaxel:** Participants may continue receiving docetaxel until PD or until a discontinuation criterion is met. Treatment in the study will continue until reaching a discontinuation criterion (defined in Section 7.1). Participants receiving pembrolizumab will be permitted to continue study treatment beyond RECIST 1.1-defined PD, as long as the treating investigator considers that the participant may experience clinical benefit with continued treatment per iRECIST, and the participant is clinically stable and tolerating study intervention, until PD is confirmed by iRECIST. All decisions to continue treatment beyond confirmed PD by iRECIST must be approved by the Sponsor. **Second Course Phase (Arm 1)** Participation in the Second Course phase is at the discretion of the investigator, according to the criteria in Section 8.10.3. **End of Treatment** Each participant will be followed for the occurrence of AEs, spontaneously reported pregnancy (Section 8.4), and survival status. Participants who discontinue for reasons other than radiographic PD will have posttreatment follow-up imaging for disease status until PD is documented radiographically per RECIST 1.1 and verified by BICR, initiating a nonstudy cancer treatment, withdrawing consent, or becoming lost to follow-up (ie, the participant is unable to be contacted by the investigator). All participants will be followed for overall survival until death, withdrawal of consent, lost to follow-up, or the end of the study. Note: Upon withdrawal of consent, the investigator will ask the participant if he or she may be contacted periodically for survival status; the participant's response will be documented in the study chart. The overall study ends when the last participant completes the last study-related contact, withdraws from the study, or is lost to follow-up.

	The study is to be discontinued based on the observation that the combination of pembrolizumab + lenvatinib versus docetaxel monotherapy 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 IA2. Upon study termination, participants are discontinued and may be enrolled in an extension study, if available.

Study Governance Committees:

Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Steering Committee	Yes

Study governance considerations are outlined in Appendix 1 (Section 10.1.1).

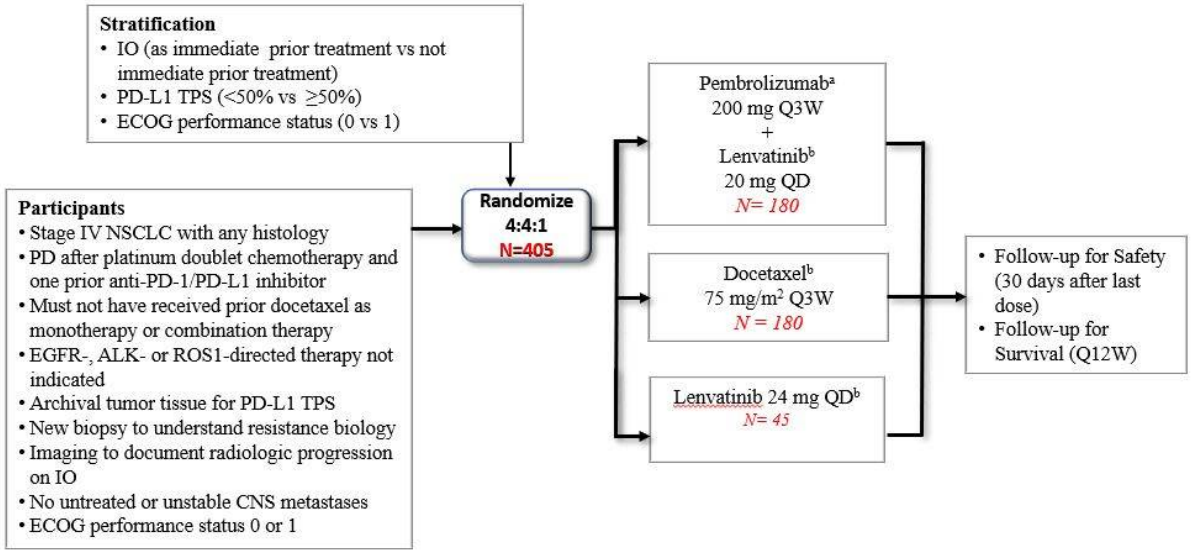
Study Accepts Healthy Participants: No

A list of abbreviations used in this document is in Appendix 10.

1.2 Schema

The study design is shown in Figure 1 (Initial Treatment) and Figure 2 (Second Course).

Figure 1 Initial Treatment

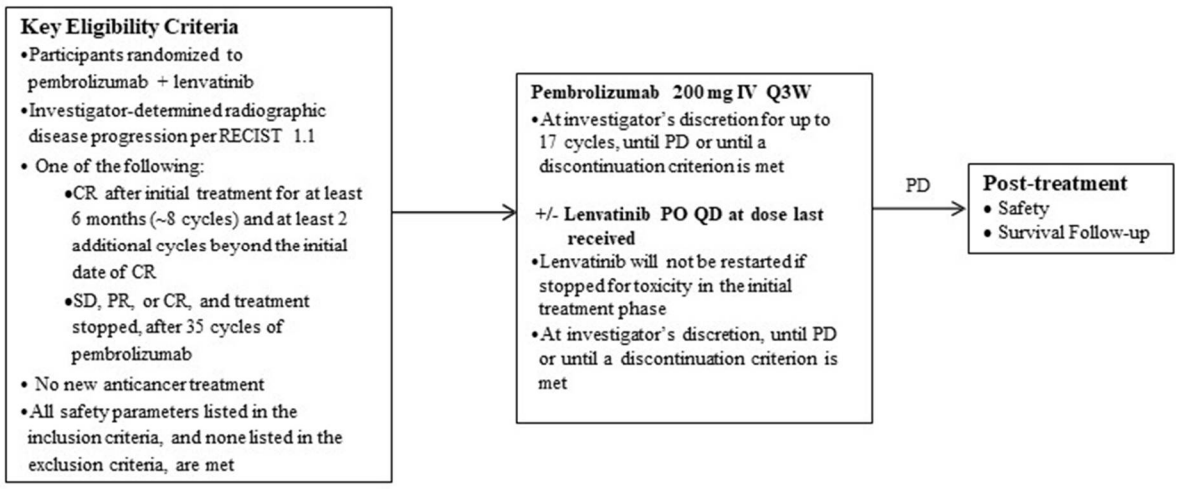


ALK = anaplastic lymphoma kinase gene; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; IO = anti-PD-1/PD-L1 treatment as immediate prior therapy versus not the immediate prior therapy NSCLC = non-small cell lung cancer; PD-1 = programmed cell death protein 1; PD-1L = programmed cell death ligand 1; Q3W = every 3 weeks; Q12W = every 12 weeks; QD = once daily; ROS1 = c-ros oncogene 1; TPS = tumor proportion score.

[a] Until disease progression, intolerable toxicity, investigator decision, or completion of 35 treatment cycles.

[b] Until disease progression, intolerable toxicity, or investigator decision.

Figure 2 Second Course



CR = complete response; IV = intravenously; PD = progressive disease; PO = orally; PR = partial response; Q3W = every 3 weeks; QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors Version 1.1.

1.3 Schedule of Activities (SoA)

1.3.1 Initial Treatment: Pembrolizumab + Lenvatinib (Arm 1) or Lenvatinib Monotherapy (Arm 3)

The same activities will apply both to participants in Arm 1 and Arm 3 unless specified in the SoA.

Trial Period	**Screening**	**Treatment Cycle = 21 days**										**EOT**	**Posttreatment**			**Notes**
													Safety FU	**FU**	**Survival FU**	
Visit Timing/ Cycle Number		**1**			**2**		**3**	**4**	**5**	**6 to 35**	**≥36**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**+3**	**+3**	**+3**	**±3**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
Administrative and General Procedures																
Informed consent	X															Documented informed consent was obtained before any protocol-specific screening procedures. Reconsent required at time of progression if study intervention is to be continued.
Inclusion/ exclusion criteria	X															
Participant identification card	X	X*														*Update with randomization number.
Demographics and medical history	X															

Trial Period	**Screening**	**Treatment Cycle = 21 days**										**EOT**	**Posttreatment**			**Notes**
													Safety FU	**FU**	**Survival FU**	
Visit Timing/ Cycle Number		**1**			**2**		**3**	**4**	**5**	**6 to 35**	**≥36**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**+3**	**+3**	**+3**	**±3**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
Prior/ concomitant medications	X	←									→					Record within 30 days before first dose of study intervention through 30 days after last dose of study intervention, or 90 days for medications for SAEs.
Prestudy anticancer therapies for NSCLC	X															
Study Intervention Administration																
Lenvatinib dispensing		X			X		X	X	X	X	X					Collect and record number of capsules returned.
Lenvatinib PO QD		←									→					Given in the clinic for Day 1 of each cycle and C1D15. See Section 8.1.8.1 for timing of lenvatinib dosing. - Taken at home QD for all additional doses.
Pembrolizumab IV Q3W		X			X		X	X	X	X						Arm 1 only.

Trial Period	**Screening**	**Treatment Cycle = 21 days**										**EOT**	**Posttreatment**			**Notes**
													Safety FU	**FU**	**Survival FU**	
Visit Timing/ Cycle Number		**1**			**2**		**3**	**4**	**5**	**6 to 35**	**≥36**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**+3**	**+3**	**+3**	**±3**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
Tumor Imaging																
Tumor imaging (chest, abdomen, and pelvis) and response assessment	X	⟷										X		X		Screening imaging within 30 days before randomization. Imaging at 6 weeks (+7 days) and 12 weeks (+7 days) from date of randomization, and then Q6W (±7 days), or more frequently if clinically indicated. After 36 weeks, imaging Q9W (±7 days). After Week 54, imaging Q12W (±7 days). Schedule should be followed regardless of treatment delays. If imaging was obtained within 4 weeks before D/C, a scan is not mandatory. FU visits may be scheduled to coincide with the imaging schedule.

Trial Period	**Screening**	**Treatment Cycle = 21 days**										**EOT**	**Posttreatment**			**Notes**
													Safety FU	**FU**	**Survival FU**	
Visit Timing/ Cycle Number		**1**			**2**		**3**	**4**	**5**	**6 to 35**	**≥36**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**+3**	**+3**	**+3**	**±3**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
Brain MRI	X															Required at screening. Within 30 days of randomization. FU MRI is required if clinically indicated. If MRI is contraindicated, or is medically inappropriate, CT with contrast is acceptable.
Efficacy Procedures																
Subsequent anticancer therapy status												X	X	X	X	Record until death or termination of survival FU. FU information may be obtained at a clinic visit, by telephone or email, or from other sources.
Survival status		←									→				X	Survival FU continues after PD, after D/C of study intervention, and after the start of new anticancer treatment. Upon Sponsor request, participants may be contacted for survival status at any time during the study.

Trial Period	**Screening**	**Treatment Cycle = 21 days**										**EOT**	**Posttreatment**			**Notes**
													Safety FU	**FU**	**Survival FU**	
Visit Timing/ Cycle Number		**1**			**2**		**3**	**4**	**5**	**6 to 35**	**≥36**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**+3**	**+3**	**+3**	**±3**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
Clinical Procedures/Assessments																
Complete physical examination	X											X				Per institutional standards.
Directed physical examination		X		X	X	X	X	X	X	X	X		X			
Contact			X													Telephone contact or visit (in-person or virtual) to assess for early toxicity. If early toxicity is suspected, an unscheduled visit may take place before C1 D15, and at any time during the study, if deemed necessary by the investigator.
Height	X															
Weight	X	X		X	X	X	X	X	X	X	X					

Trial Period	**Screening**	**Treatment Cycle = 21 days**										**EOT**	**Posttreatment**			**Notes**
													Safety FU	**FU**	**Survival FU**	
Visit Timing/ Cycle Number		**1**			**2**		**3**	**4**	**5**	**6 to 35**	**≥36**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**+3**	**+3**	**+3**	**±3**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
Vital signs	X	X		X*	X	X*	X	X	X	X	X	X	X			*D15 visits mandatory for C1 and C2. C3 and subsequent cycles, participants may return on D15 if BP monitoring is required. Refer to Section 6.6.2.1 for hypertension management and BP monitoring guidelines.

Trial Period	**Screening**	**Treatment Cycle = 21 days**										**EOT**	**Posttreatment**			**Notes**
													Safety FU	**FU**	**Survival FU**	
Visit Timing/ Cycle Number		**1**			**2**		**3**	**4**	**5**	**6 to 35**	**≥36**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**+3**	**+3**	**+3**	**±3**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
12-lead ECG with QTcF determination	X	X^			X^					X*	X*	X	X			*Every 4 cycles (12 weeks) after C2, or at every cycle if clinically indicated. ^ For the first 90 subjects in Arm 1 assigned to have PK samples drawn: 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 monitoring every cycle. If lenvatinib is discontinued, ECGs are only required at the EOT and Safety Follow-up visits.
MUGA scan or ECHO	X											X				Additional LVEF assessments as clinically indicated.

Trial Period	**Screening**	**Treatment Cycle = 21 days**										**EOT**	**Posttreatment**			**Notes**
													Safety FU	**FU**	**Survival FU**	
Visit Timing/ Cycle Number		**1**			**2**		**3**	**4**	**5**	**6 to 35**	**≥36**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**+3**	**+3**	**+3**	**±3**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
ECOG performance status	X	X*			X		X	X	X	X	X	X	X			*Within 7 days before first dose of study drug on, or, before randomization for all subjects. If C1D1 is the same day as randomization, C1D1 ECOG will be used as the ECOG value for randomization/IVR.
AE/SAE review	X	←										→	X*	X		*Report NSAEs occurring within 30 days after the last dose of study intervention, regardless of initiation of new therapy. Report SAEs occurring within 90 days after the last dose of study intervention, or within 30 days after the last dose of study intervention if new anticancer therapy is initiated.

Trial Period	**Screening**	**Treatment Cycle = 21 days**										**EOT**	**Posttreatment**			**Notes**
													Safety FU	**FU**	**Survival FU**	
Visit Timing/ Cycle Number		**1**			**2**		**3**	**4**	**5**	**6 to 35**	**≥36**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**+3**	**+3**	**+3**	**±3**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
Laboratory Procedures/Assessments (Local Laboratory)																
Pregnancy test: urine or serum β-HCG (WOCBP only)	X				X		X	X	X	X	X	X	X			Urine test within 24 hours or serum test within 72 hours before the first dose of study intervention. Additional urine/serum testing if clinically warranted and/or defined by local regulations (See Appendix 7). Serum test required if urine test cannot be confirmed as negative.
HIV and hepatitis B/C	X															Only if mandated by local health authority (See Appendix 7).
Serum FSH (WONCBP only)	X															In the absence of 12 months of amenorrhea, confirmation with 2 FSH values at least 24 hours apart in postmenopausal range is required.

Trial Period	**Screening**	**Treatment Cycle = 21 days**										**EOT**	**Posttreatment**			**Notes**
													Safety FU	**FU**	**Survival FU**	
Visit Timing/ Cycle Number		**1**			**2**		**3**	**4**	**5**	**6 to 35**	**≥36**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**+3**	**+3**	**+3**	**±3**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
CBC with differential	X			X	X		X	X	X	X	X	X	X			At screening, within 10 days before first dose. After C1, within 3 days before dosing; every effort should be made to collect samples at the same time of day.
Clinical chemistry	X			X	X		X	X	X	X	X	X	X			
Urinalysis/ Urine dipstick testing	X			X	X	X	X	X	X	X	X	X	X			At screening, complete urinalysis is required within 10 days before first dose and every 6 cycles At other visits, either urinalysis or urine dip stick are acceptable (refer to Section 8.3.5.1.2). -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 in Section 8.3.5.1.2.

Trial Period	**Screening**	**Treatment Cycle = 21 days**										**EOT**	**Posttreatment**			**Notes**
													Safety FU	**FU**	**Survival FU**	
Visit Timing/ Cycle Number		**1**			**2**		**3**	**4**	**5**	**6 to 35**	**≥36**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**+3**	**+3**	**+3**	**±3**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
PT/INR and aPTT/PTT	X															Within 10 days before first dose. Additional testing as clinically indicated for participants taking anticoagulants.
T3 or FT3, FT4, TSH	X				X			X		X*	X*	X				Within 10 days before first dose. *After screening, within 3 days before dosing at every other cycle, beginning with C2. Participants may be dosed while test results are pending. FT3 is acceptable if T3 cannot be determined. The central laboratory may be used only if the local laboratory cannot perform tests.
PK/Biomarkers (Central Laboratory)																
Blood for genetic analysis		X														Predose.

Trial Period	**Screening**	**Treatment Cycle = 21 days**										**EOT**	**Posttreatment**			**Notes**
													Safety FU	**FU**	**Survival FU**	
Visit Timing/ Cycle Number		**1**			**2**		**3**	**4**	**5**	**6 to 35**	**≥36**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**+3**	**+3**	**+3**	**±3**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
Serum for pembrolizumab PK: first 90 participants in Arm 1		X			X					*X						Predose on C1D1, C2D1, and *C8D1.
Serum anti-pembrolizumab antibodies: first 90 participants in Arm 1		X			X					*X						Predose on C1D1, C2D1, and *C8D1.

Trial Period	**Screening**	**Treatment Cycle = 21 days**										**EOT**	**Posttreatment**			**Notes**
													Safety FU	**FU**	**Survival FU**	
Visit Timing/ Cycle Number		**1**			**2**		**3**	**4**	**5**	**6 to 35**	**≥36**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**+3**	**+3**	**+3**	**±3**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
Plasma for lenvatinib PK: first 90 participants in Arm 1		X		X	X											C1D1: postdose at any time from 0.5 to 4 hours and from 6 to 10 hours postdose (2 samples). C1D15: predose within 2 hours of lenvatinib dosing and then at any time from 2 to 12 hours postdose (2 samples). C2D1: predose within 2 hours of lenvatinib dosing and then at any time from 0.5 to 4 hours and from 6 to 10 hours postdose (3 samples). Note: No PK samples if lenvatinib dosing is on hold for any reason.
Blood for plasma biomarker analyses (Arm 1 and Arm 3)		X			X		X		X	X*		X				Predose. *D1 of every 3 cycles after C5.

Trial Period	**Screening**	**Treatment Cycle = 21 days**										**EOT**	**Posttreatment**			**Notes**
													Safety FU	**FU**	**Survival FU**	
Visit Timing/ Cycle Number		**1**			**2**		**3**	**4**	**5**	**6 to 35**	**≥36**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**+3**	**+3**	**+3**	**±3**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
Blood for serum biomarker analyses (Arm 1 and Arm 3)		X		X	X		X		X			X				Predose.
Blood for RNA analysis (Arm 1 and Arm 3)		X			X		X		X			X				Predose.
Blood for circulating tumor nucleic acids (Arm 1 and Arm 3)		X			X		X		X	X*		X				Predose. *D1 of every 3 cycles after C5.
Tumor Tissue Collection																
Archival tumor tissue	X															To central laboratory before randomization for PD-L1 analysis and stratification. See Section 8.2.1.8 for window for obtaining tissue.

Trial Period	**Screening**	**Treatment Cycle = 21 days**										**EOT**	**Posttreatment**			**Notes**
													Safety FU	**FU**	**Survival FU**	
Visit Timing/ Cycle Number		**1**			**2**		**3**	**4**	**5**	**6 to 35**	**≥36**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**+3**	**+3**	**+3**	**±3**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
Newly obtained tissue biopsy	X															To central laboratory before randomization. No anticancer treatment between biopsy and randomization. See Section 8.2.1.8 for window for obtaining tissue.
EGFR, ALK, and ROS1 molecular status	X															Not required in squamous NSCLC. Tumor tissue may be sent to central laboratory for molecular testing if status is unknown and cannot be determined locally.

Trial Period	**Screening**	**Treatment Cycle = 21 days**										**EOT**	**Posttreatment**			**Notes**
													Safety FU	**FU**	**Survival FU**	
Visit Timing/ Cycle Number		**1**			**2**		**3**	**4**	**5**	**6 to 35**	**≥36**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**+3**	**+3**	**+3**	**±3**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
Patient-Reported Outcomes																
EORTC QLQ-C30		X			X		X	X	X	X*		X	X			Administer questionnaires before any procedures in the order in this table. *Obtain at every cycle through C17, then at every other cycle until EOT. If the EOT visit takes place ≥30 days after the last dose of study intervention and is combined with the 30-day safety FU visit, PRO assessments only need to be performed at that visit.
EORTC QLQ-LC13		X			X		X	X	X	X*		X	X			
EQ-5D-5L		X			X		X	X	X	X*		X	X			

Abbreviations: AE = adverse event; ALK = anaplastic lymphoma kinase gene; aPTT = activated partial thromboplastin time; BP = blood pressure; β-HCG = β human chorionic gonadotropin; CBC = complete blood count; CT = computed tomography; CXDY= Cycle X Day Y; D/C = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor gene; ECHO = echocardiogram; EORTC = European Organization for Research and Treatment of Cancer; EOT = end of treatment; EQ-5D-5L = European Quality of Life Five-Dimensional Five-Level Scale Questionnaire; FSH = follicle-stimulating hormone; FT3 = free triiodothyronine; FT4 = free thyroxine; FU = follow-up; HIV = human immunodeficiency virus; INR = international normalized ratio; IV = intravenous; IVR = Interactive Voice Response; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NSCLC = non-small cell lung cancer; PD = progressive disease; PD-L1 = programmed cell death ligand 1; PK = pharmacokinetics; PO = oral; PT = prothrombin time; PRO = patient-reported outcome; Q3W = every 3 weeks; Q6W = every 6 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; QD = once daily; QLQ-C30 = Quality of Life Questionnaire Core 30 items; QLQ-LC13 = Quality of Life Questionnaire Lung Cancer Module 13; QTcF = QT interval corrected with Fridericia's formula; RNA = ribonucleic acid; ROS1 = c-ros oncogene 1; SAE = serious adverse event; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential; WONCBP = women of non-childbearing potential.

1.3.2 Initial Treatment: Docetaxel (Arm 2)

Trial Period	**Screening**	**Treatment Cycle = 21 days**						**Posttreatment**				**Notes**
								EOT	**Safety FU**	**FU**	**Survival FU**	
Visit Timing/Cycle Number		**1**	**2**	**3**	**4**	**5**	**6 and beyond**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
Administrative and General Procedures												
Informed consent	X											Documented informed consent was obtained before any protocol-specific screening procedures. Reconsent required at time of progression if study intervention is to be continued.
Inclusion/ exclusion criteria	X											
Participant identification card	X	X*										*Update with randomization number.
Demographics and medical history	X											
Prior/ concomitant medications	X	←							→			Record within 30 days before first dose of study intervention through 30 days after last dose of study intervention, or 90 days for medications for SAEs.
Prestudy anticancer therapies for NSCLC	X											

Trial Period	Screening	Treatment Cycle = 21 days						Posttreatment				Notes
								EOT	Safety FU	FU	Survival FU	
Visit Timing/Cycle Number		**1**	**2**	**3**	**4**	**5**	**6 and beyond**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
Study Intervention Administration												
Docetaxel IV Q3W		X	X	X	X	X	X					
Tumor Imaging												
Tumor imaging (chest, abdomen, and pelvis) and response assessment	X	⟷						X		X		Screening imaging within 30 days before randomization. Imaging at 6 weeks (+7 days) and 12 weeks (+7 days) from date of randomization, and then Q6W (±7 days), or more frequently if clinically indicated. After 36 weeks, imaging Q9W (±7 days). After Week 54, imaging Q12W (±7 days). Schedule should be followed regardless of treatment delays. If imaging was obtained within 4 weeks before D/C, a scan is not mandatory. FU visits may be scheduled to coincide with the imaging schedule.
Brain MRI	X											Required at screening. Within 30 days of randomization. FU MRI is required if clinically indicated. If MRI is contraindicated, or is medically inappropriate, CT with contrast is acceptable.

Trial Period	**Screening**	**Treatment Cycle = 21 days**						**Posttreatment**				**Notes**
								EOT	**Safety FU**	**FU**	**Survival FU**	
Visit Timing/Cycle Number		**1**	**2**	**3**	**4**	**5**	**6 and beyond**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
Efficacy Procedures												
Subsequent anticancer therapy status								X	X	X	X	Record until death or termination of survival FU. FU information may be obtained at a clinic visit, by telephone or email, or from other sources.
Survival status		←									→	X	Survival FU continues after PD, after D/C of study intervention, and after the start of new anticancer treatment. Upon Sponsor request, participants may be contacted for survival status at any time during the study.
Clinical Procedures/Assessments												
Complete physical examination	X							X				Per institutional standards.
Directed physical examination		X	X	X	X	X	X		X			
Height	X											
Weight	X	X	X	X	X	X	X					Calculate BSA.
Vital signs	X	X	X	X	X	X	X	X	X			
12-lead ECG with QTcF determination	X											
MUGA scan or ECHO	X											Additional LVEF assessments as clinically indicated.

Trial Period	**Screening**	**Treatment Cycle = 21 days**						**Posttreatment**				**Notes**
								EOT	**Safety FU**	**FU**	**Survival FU**	
Visit Timing/Cycle Number		**1**	**2**	**3**	**4**	**5**	**6 and beyond**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
ECOG performance status	X	X*	X	X	X	X	X	X	X			*Within 7 days before first dose of study drug and before randomization for all subjects. If C1D1 is the same day as randomization, C1D1 ECOG will be used as the ECOG value for enrollment/IVR.
AE/SAE review	X	⟷							X*	X		*Report NSAEs occurring within 30 days after the last dose of study intervention, regardless of initiation of new therapy. Report SAEs occurring within 90 days after the last dose of study intervention, or within 30 days after the last dose of study intervention if new anticancer therapy is initiated.
Laboratory Procedures/Assessments (Local Laboratory)												
Pregnancy test: urine or serum β-HCG (WOCBP only)	X		X	X	X	X	X	X	X			Urine test within 24 hours or serum test within 72 hours before the first dose of study intervention. Additional urine/serum testing if clinically warranted and/or defined by local regulations (Appendix 7). Serum test required if urine test cannot be confirmed as negative.
HIV and hepatitis B/C	X											Only if mandated by local health authority (Appendix 7).
Serum FSH (WONCBP only)	X											In the absence of 12 months of amenorrhea, confirmation with 2 FSH values at least 24 hours apart in postmenopausal range is required.

Trial Period	Screening	Treatment Cycle = 21 days						Posttreatment				Notes
								EOT	Safety FU	FU	Survival FU	
Visit Timing/Cycle Number		**1**	**2**	**3**	**4**	**5**	**6 and beyond**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
CBC with differential	X		←	—	—	—	→	X	X			At screening, within 10 days before first dose.
Clinical chemistry	X		←	—	—	—	→	X	X			After C1, within 3 days before dosing; every effort should be made to collect samples at the same time of day.
Urinalysis	X						X*	X	X			At screening, within 10 days before first dose. *At C6 and then every 6 cycles within 3 days before D1.
PT/INR and aPTT/PTT	X											At screening, within 10 days before first dose.
T3 or FT3, FT4, TSH	X											
Biomarkers (Central Laboratory)												
Blood for genetic analysis		X										Predose.
Blood for plasma biomarker analyses		X	X	X		X	X*	X				Predose. *D1 of every 3 cycles after C5.
Blood for serum biomarker analyses		X	X	X		X		X				Predose.
Blood for RNA analysis		X	X	X		X		X				Predose.

Trial Period	Screening	Treatment Cycle = 21 days						Posttreatment				Notes
								EOT	Safety FU	FU	Survival FU	
Visit Timing/Cycle Number		**1**	**2**	**3**	**4**	**5**	**6 and beyond**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
Blood for circulating tumor nucleic acids		X	X	X		X	X*	X				Predose. *D1 of every 3 cycles after C5.
Tumor Tissue Collection												
Archival tumor tissue	X											To central laboratory before randomization for PD-L1 analysis and stratification. See Section 8.2.1.8 for window for obtaining tissue.
Newly obtained tissue biopsy	X											To central laboratory before randomization. No anticancer treatment between biopsy and randomization. See Section 8.2.1.8 for window for obtaining tissue.
EGFR, ALK, and ROS1 molecular status	X											Not required in squamous NSCLC. Tumor tissue may be sent to central laboratory for molecular testing if status is unknown and cannot be determined locally.

Trial Period	Screening	Treatment Cycle = 21 days						Posttreatment				Notes
								EOT	Safety FU	FU	Survival FU	
Visit Timing/Cycle Number		**1**	**2**	**3**	**4**	**5**	**6 and beyond**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Cycle Day		**1**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
Patient-Reported Outcomes												
EORTC QLQ-C30		X	X	X	X	X	X*	X	X			Administer questionnaires before any procedures in the order in this table. *Obtain at every cycle through C17, then at every other cycle until EOT. If the EOT visit takes place ≥30 days after the last dose of study intervention and is combined with the 30-day safety FU visit, PRO assessments only need to be performed at that visit.
EORTC QLQ-LC13		X	X	X	X	X	X*	X	X			
EQ-5D-5L		X	X	X	X	X	X*	X	X			

Abbreviations: AE = adverse event; ALK = anaplastic lymphoma kinase gene; aPTT = activated partial thromboplastin time; β-HCG = β human chorionic gonadotropin; BSA = body surface area; CBC = complete blood count; CT = computed tomography; CXDY= Cycle X Day Y; D/C = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor gene; ECHO = echocardiogram; EORTC = European Organization for Research and Treatment of Cancer; EOT = end of treatment; EQ-5D-5L = European Quality of Life Five-Dimensional Five-Level Scale Questionnaire; FSH = follicle-stimulating hormone; FT3 = free triiodothyronine; FT4 = free thyroxine; FU = follow-up; HIV = human immunodeficiency virus; INR = international normalized ratio; IVR = Interactive Voice Response; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NSAE = nonserious adverse event; NSCLC = non-small cell lung cancer; PD = progressive disease; PD-L1 = programmed cell death ligand 1; PK = pharmacokinetics; PT = prothrombin time; PRO = patient-reported outcome; Q3W = every 3 weeks; Q6W = every 6 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; QD = once daily; QLQ-C30 = Quality of Life Questionnaire Core 30 items; QLQ-LC13 = Quality of Life Questionnaire Lung Cancer Module 13; QTcF = QT interval corrected with Fridericia's formula; RNA = ribonucleic acid; ROS1 = c-ros oncogene 1; SAE = serious adverse event; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential; WONCBP = women of non-childbearing potential.

1.3.3 Second Course (Arm 1 – Retreatment)

Trial Period	Treatment Cycle = 21 days							EOT	Posttreatment			Notes
									Safety Follow-up[a]	Follow-up[b]	Survival Follow-up	
Visit Timing/ Cycle Number	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**≥18**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Scheduling Window (days)	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
Administrative and General Procedures												
Inclusion/exclusion criteria	X											All safety parameters listed in the inclusion criteria, and none listed in the exclusion criteria, are met.
Eligibility criteria	X											
Concomitant medications	X	X	X	X	X	X	X	X	X			Record within 30 days before first dose of study intervention through 30 days after last dose of study intervention, or 90 days for medications for SAEs.
Study Intervention Administration												
Lenvatinib dispensing	X	X	X	X	X	X	X					Collect and record number of capsules returned.
Lenvatinib PO QD at dose level last received	X	X	X	X	X	X	X					The decision to continue lenvatinib will be at the discretion of the investigator. If continued, the first dose will be given in the clinic just after the pembrolizumab infusion. If pembrolizumab is discontinued, lenvatinib will be given in the clinic on D1 of each cycle and taken at home on all other days. Lenvatinib treatment will continue until a discontinuation criterion is met.
Pembrolizumab IV Q3W	X	X	X	X	X	X						Eligible participants may receive up to 17 additional treatment cycles of pembrolizumab.

Trial Period	**Treatment Cycle = 21 days**							**EOT**	**Posttreatment**			**Notes**
									Safety Follow-up[a]	**Follow-up[b]**	**Survival Follow-up**	
Visit Timing/ Cycle Number	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**≥18**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Scheduling Window (days)	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
Efficacy Procedures												
Tumor imaging (chest, abdomen, and pelvis) and response assessment	X	←					→	X		X*		Baseline imaging is the scan showing PD that indicates treatment is necessary. Perform within 30 days before C1. Q12W (±7 days) from C1. This schedule should be followed regardless of treatment delays. If imaging was obtained within 4 weeks before D/C, a scan at D/C is not mandatory. *FU visits may be scheduled to coincide with the imaging schedule.
Efficacy Procedures												
Subsequent anticancer therapy status								X	X	X	X	Record until death or termination of survival FU. FU information may be obtained at a clinic visit or by telephone, email, or other sources.
Survival status	←						→				X	Survival FU continues after PD, after discontinuation of study intervention, and after the start of new anticancer treatment. Upon Sponsor request, participants may be contacted for survival status at any time during the study.
Clinical Procedures/Assessments												
Complete physical examination	X							X				Per institutional standards.
Directed physical examination		X	X	X	X	X	X		X			

Trial Period	**Treatment Cycle = 21 days**							**EOT**	**Posttreatment**			**Notes**
									Safety Follow-up[a]	**Follow-up[b]**	**Survival Follow-up**	
Visit Timing/ Cycle Number	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**≥18**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Scheduling Window (days)	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
Vital signs; weight	X	X	X	X	X	X	X	X	X			Refer to Section 6.6.2.1 for hypertension management and BP monitoring guidelines.
12-lead ECG with QTcF determination	X	X				X*	X*	X	X			*Every 4 cycles (12 weeks) after C2. For high-risk patients (as defined in Section 8.3.3), conduct monitoring every cycle. If lenvatinib is discontinued, ECGs are only required at the EOT and Safety Follow-up visits.
ECOG performance status	X*	X	X	X	X	X	X	X				*Within 7 days prior to C1.
AE/SAE review	⟷								X*	X		Report NSAEs occurring within 30 days after the last dose of study intervention, regardless of initiation of new therapy. *Report SAEs occurring within 90 days after the last dose of study intervention, or within 30 days after the last dose of study intervention if a new anticancer therapy is initiated.
Laboratory Procedures/Assessments (Local Laboratory)												
Pregnancy test: urine or serum β-HCG (WOCBP only)	X	X	X	X	X	X	X	X	X			Urine test within 24 hours or serum test within 72 hours before C1. Additional urine/serum testing if clinically warranted and/or as defined by local regulations (see Appendix 7). Serum test required if urine test cannot be confirmed as negative.

Trial Period	Treatment Cycle = 21 days							EOT	Posttreatment			Notes
									Safety Follow-up[a]	Follow-up[b]	Survival Follow-up	
Visit Timing/ Cycle Number	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**≥18**	**At D/C**	**30 days after last dose**	**Q12W**	**Q12W**	**All procedures are performed before administration of study intervention unless otherwise indicated.**
Scheduling Window (days)	**-**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**–**	**+7**	**±7**	**±14**	
CBC with differential	X	X	X	X	X	X	X	X	X			Within 10 days before C1. After C1, within 3 days before dosing; every effort should be made to collect samples at the same time of day.
Clinical chemistry	X	X	X	X	X	X	X	X	X			
Urinalysis/ Urine dipstick testing (participants taking lenvatinib)	X	X	X	X	X	X	X	X	X			Complete urinalysis is required within 10 days of C1 and every 6 cycles during pembrolizumab treatment. At other visits, either urinalysis or urine dip stick are acceptable while taking lenvatinib (refer to Section 8.3.5.1.2).
PT/INR and aPTT/PTT	X											Additional testing as clinically indicated for participants taking anticoagulants.
T3 or FT3, FT4, and TSH	X	X		X		X*	X*	X				Within 10 days before C1. *After C1, within 3 days before dosing at every other cycle, beginning with C2. Participants may be dosed while test results are pending. FT3 is acceptable if T3 cannot be determined. The central laboratory may be used only if the local laboratory cannot perform these tests.

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; β-HCG = beta human chorionic gonadotropin; BP = blood pressure; CBC = complete blood count; CXDY = Cycle X Day Y; D/C = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FT3 = free triiodothyronine; FT4 = free thyroxine; FU = follow-up; INR = international normalized ratio; IV = intravenous; NSAE = nonserious adverse event; PD = progressive disease; PO = oral; PT = prothrombin time; PTT = partial thromboplastin time; Q3W = every 3 weeks; Q12W = every 12 weeks; QD = once daily; QTc = QT interval corrected with Fridericia's formula; SAE = serious adverse event;T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; W = weeks; WOCBP = women of childbearing potential.

[a] If the discontinuation visit is ≥30 days from the last dose of study intervention, the 30-day safety FU visit is not required.

[b] For participants discontinuing treatment for reasons other than PD, FU visits and imaging will continue until PD or initiation of new anticancer therapy. Participants discontinuing treatment with PD will proceed directly to survival FU.

2 INTRODUCTION

Lenvatinib (also known as E7080 or MK-7902; hereafter referred to as lenvatinib) inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib inhibits other kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; platelet derived growth factor receptor alpha (PDGFRα), KIT, and RET. Lenvatinib also exhibited antiproliferative activity in cell lines dependent on activated FGFR signaling with a concurrent inhibition of FGF-receptor substrate 2α phosphorylation. Once daily (QD) dosing of lenvatinib combined with pembrolizumab is currently being developed for the treatment of metastatic NSCLC.

2.1 Study Rationale

The global incidence of lung cancer was 1.8 million cases 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 patients with NSCLC, tumor histology is approximately 40% to 60% adenocarcinoma, 10% to 15% squamous, and 5% neuroendocrine, and the rest is 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. The 5-year relative survival for patients with any lung cancer overall, and metastatic lung cancer specifically, has been reported to be 17.7% and 4.3%, respectively [National Cancer Institute 2016].

The therapeutic landscape in metastatic NSCLC has dramatically changed with approvals of immunotherapy agents in both treatment-naïve and previously treated cancer, irrespective of histology. In previously treated patients with advanced NSCLC, immune-checkpoint inhibitors targeting the programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) pathway (pembrolizumab, nivolumab, and atezolizumab) have proven benefits for survival over the standard chemotherapy, docetaxel [Borghaei, H., et al 2015] [Brahmer, J., et al 2015] [Herbst, R. S., et al 2016] [Rittmeyer, A., et al 2017].

The results from the KEYNOTE-001 and KEYNOTE-010 studies demonstrated that pembrolizumab provided substantial, clinically meaningful benefits in OS, progression-free survival (PFS), and objective response rate (ORR) in patients with NSCLC whose disease progressed after platinum-containing chemotherapy and whose tumor cells expressed PD-L1. Based on these 2 studies, pembrolizumab monotherapy is approved for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (tumor proportion score [TPS] ≥1%), with PD during or after platinum-containing chemotherapy. In addition, the National Comprehensive Cancer Network Guidelines recommend immune-checkpoint inhibitors as the preferred agent for subsequent therapy in patients with metastatic NSCLC based on improved survival rates, longer duration of response, and fewer AEs compared with cytotoxic chemotherapy [National Comprehensive Cancer Network 2018].

The results from KEYNOTE-024 established pembrolizumab monotherapy as first-line (1L) therapy for patients whose tumors have TPS ≥50% and no EGFR or ALK genomic aberrations. Approximately 30% of patients with newly diagnosed advanced NSCLC highly express PD-L1 to TPS ≥50% [Reck, M., et al 2016]. Additionally, KEYNOTE-042 compared pembrolizumab monotherapy to standard of care (SOC) platinum-based chemotherapy in previously untreated participants with advanced or metastatic NSCLC whose tumors expressed PD-L1 with TPS ≥1%. The study confirmed the OS treatment effect of pembrolizumab monotherapy observed in participants with TPS ≥50% NSCLC in KEYNOTE-024, and it extended these benefits to a broader population with TPS ≥1% NSCLC.

Two recently completed studies, KEYNOTE-189 and KEYNOTE-407, demonstrated a statistically significant and clinically meaningful improvement in OS, PFS, and ORR with pembrolizumab in combination with platinum doublet chemotherapy compared with chemotherapy alone in nonsquamous and squamous NSCLC, irrespective of PD-L1 tumor expression [Gandhi, L., et al 2018] [Paz-Ares, L., et al 2018].

Lenvatinib is a multi-receptor tyrosine kinase inhibitor that inhibits the kinase activities of VEGF and its family of receptors (VEGFRs 1-3). Lenvatinib also inhibits other receptor tyrosine kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression.

Lenvatinib has been studied as both monotherapy and in combination with chemotherapy for the treatment of advanced NSCLC. For monotherapy, a randomized Phase 2 study (E7080-703), 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 of lenvatinib QD and 46 received placebo; all participants received best supportive care in addition to study treatment. Median OS was 34.8 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. Grade 3 and/or 4 AEs occurred in 69% of lenvatinib recipients, and in 50% of placebo recipients. Grade 3 and/or 4 AEs were dyspnea and pneumonia in both treatment groups, as well as hypertension in the lenvatinib group [Havel, L., et al 2014].

Based on these results, an open-label, Phase 1b/2 study (Study 111/KEYNOTE 146) to assess the safety and preliminary antitumor activity of the combination of lenvatinib plus pembrolizumab in participants with selected solid tumors was initiated (see Section 2.2.3 Ongoing Clinical Studies).

There is a large unmet medical need for safe and effective therapy for patients who have PD after platinum doublet chemotherapy and acquired resistance to immunotherapy. Although immunotherapy is a true paradigm shift in 1L and second-line (2L) treatment of patients with metastatic NSCLC, it is plausible that pembrolizumab in combination with lenvatinib could lead to a greater depth of response and an increase in OS. The current study is designed to further evaluate the safety and efficacy of combination therapy with pembrolizumab + lenvatinib versus docetaxel. The outcomes for patients in this study would be further

improved if the safety profile of pembrolizumab + lenvatinib remains acceptable and is shown to improve outcomes compared with docetaxel; therefore, this study could support regulatory approval of the combination in this population.

While docetaxel is an accepted 2L SOC treatment for patients with NSCLC, the ORR is approximately 5% to 10%, median PFS is approximately 3 months, and median OS is approximately 7.5 months [Fossella, F. V., et al 2000] [Shepherd, F. A., et al 2000] [Hanna, N., et al 2004]. Improvements in OS are needed, since no patient with progressive NSCLC is cured.

2.2 Background

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 Inhibition of VEGFR as a Target for Cancer Treatment (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 (VEGFRs 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 in 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 RTKi that selectively inhibits VEGF receptors, VEGFR1 (FLT1), VEGFR2 (KDR), VEGFR3 (FLT4), FGFR1-4, PDGFRα, c-kit, and RET. Among known kinase inhibitors in clinical use, lenvatinib is one of the only inhibitors currently labeled with action as an inhibitor of not only VEGFRs but also FGFRs, both of which are currently believed to be very important for tumor angiogenesis.

Lenvatinib inhibited cell free kinase activities for VEGFR1-3 and FGFR1-3 with Ki values around 1 nmol/L, and 8-22 nmol/L, respectively [Yamamoto, Y., et al 2014]. In cell-based assays, lenvatinib inhibited VEGF-derived and FGF-derived tube formation of human umbilical vein endothelial cell (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 (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. Refer to the Investigator's Brochure (IB) [IB Edition 15-Eisai 2018] for detailed background information on lenvatinib.

2.2.1.2 Inhibition of PD-1 as a Target for Cancer Treatment (Pembrolizumab)

Pembrolizumab is a potent humanized immunoglobulin G4 monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (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 intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications, including NSCLC. For more details on specific indications refer to the IB [IB Edition 16 2018] and the approved product label [U.S. Prescribing Information 2018].

2.2.1.3 Scientific Rationale for the Combination of Pembrolizumab With Lenvatinib

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

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

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 IV every 3 weeks (Q3W). The safety and efficacy of the combination at the lenvatinib RP2D is being assessed in the Phase 2 portion of the study that includes 6 cohorts (ie, NSCLC, renal cell carcinoma [RCC], endometrial cancer, urothelial carcinoma, melanoma, and squamous cell carcinoma of the head and neck).

2.2.1.4 Rationale for Lenvatinib Monotherapy Arm

A randomized lenvatinib arm (Arm 3) was added to the study design to assess the contribution of lenvatinib in the overall treatment effect of the combination of pembrolizumab + lenvatinib.

2.2.2 Preclinical and Clinical Studies

2.2.2.1 Completed Studies With Pembrolizumab and Lenvatinib

Refer to the respective IBs for pembrolizumab [IB Edition 15 2017] and lenvatinib [IB Edition 15-Eisai 2018] for additional preclinical and clinical study data for pembrolizumab and lenvatinib.

2.2.3 Ongoing Clinical Studies of Pembrolizumab and Lenvatinib

Pembrolizumab is under evaluation in patients with NSCLC as monotherapy and in combination with chemotherapy, immunotherapy, and targeted therapies. Lenvatinib is undergoing studies in patients with different types of solid tumors, including NSCLC, in combination with other therapies including PD-1 targeted therapies. Full lists of ongoing studies are in the respective IBs for pembrolizumab and lenvatinib.

Study 111/KEYNOTE-146

Study 111/KEYNOTE-146 is a multicenter, open-label, Phase 1b/2 clinical trial being conducted to evaluate the efficacy and safety of lenvatinib in combination with pembrolizumab. Phase 1b of this study determined the MTD and RP2D of lenvatinib as 20 mg QD in combination with 200 mg of pembrolizumab IV Q3W. The safety and efficacy of the combination at the lenvatinib RP2D is being assessed in the Phase 2 portion of the study that includes 6 cohorts (ie, NSCLC, renal cell carcinoma [RCC], endometrial cancer, urothelial carcinoma, melanoma, and squamous cell carcinoma of the head and neck).

As of 01-MAR-2018, a total of 21 participants with metastatic NSCLC were enrolled in the Phase 2 portion of Study 111/KEYNOTE-146. Participants in the Phase 2 portion of the study received lenvatinib 20 mg orally once daily plus pembrolizumab 200 mg intravenously once every 3 weeks. ORR after 24 weeks of treatment was 33.3%. The best overall response (BOR) was complete response (CR) in 1 participant (4.8%), partial response (PR) in 6 (28.6%), stable disease(SD) in 10 (47.6%), and PD in 2 (9.5%). In 2 participants the BOR was unknown or not evaluable. Median PFS was 5.9 months. Grade 3 and Grade 4 treatment-related AEs occurred in 11 participants (52.4%). The most common Grade 3 treatment-related AEs were hypertension (19%), fatigue (14%), diarrhea (14%), proteinuria (10%), and

arthralgia (10%). There was 1 death (exsanguination) considered possibly treatment-related [Brose, M., et al 2018].

Based on Study 111/KEYNOTE-146, lenvatinib 20 mg QD in combination with pembrolizumab 200 mg IV Q3W was the dose selected for this Phase 3 study.

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.

With the approval of immune-checkpoint inhibitors targeting the PD-1/PD-L1 pathway as a 1L therapy for NSCLC, there is an unmet medical need for safe and efficacious 2L + therapy in patients whose disease has progressed with 1L treatment. The existing data suggest that inhibiting angiogenesis in combination with PD-1 blockade is a promising therapeutic strategy, and the benefit/risk assessment for patients in this study is favorable, making the combination of pembrolizumab + lenvatinib a promising 2L+ therapeutic option in patients with metastatic squamous or nonsquamous NSCLC and no *EGFR* or *ALK* tumor genome aberrations, regardless of PD-L1 expression.

Additional details regarding specific benefits and risks for participants in this study are in the accompanying IBs and ICFs.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

In participants with metastatic NSCLC and PD after platinum doublet chemotherapy and treatment with 1 prior anti-PD-1/PD-L1 monoclonal antibody (mAb):

Note: Progression-free survival (PFS), objective response rate (ORR), duration of response (DOR), and disease control rate at 12 weeks (DCR12) will be assessed per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

Primary Objective	**Primary Endpoint**
To compare pembrolizumab + lenvatinib to docetaxel with respect to overall survival (OS). Hypothesis (H1): Pembrolizumab + lenvatinib prolongs OS compared with docetaxel.	OS, defined as the time from randomization to the date of death due to any cause.
To compare pembrolizumab + lenvatinib to docetaxel with respect to PFS per RECIST 1.1 by blinded independent central review (BICR). Hypothesis (H2): Pembrolizumab + lenvatinib prolongs PFS per RECIST 1.1 based on BICR compared with docetaxel.	PFS, defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurs first.
Secondary Objectives	**Secondary Endpoints**
To compare pembrolizumab + lenvatinib to docetaxel with respect to ORR per RECIST 1.1 by BICR. Hypothesis (H3): Pembrolizumab + lenvatinib results in a superior ORR per RECIST 1.1 based on BICR compared with docetaxel.	Objective response, defined as a confirmed complete response (CR) or partial response (PR).
To compare pembrolizumab + lenvatinib to lenvatinib monotherapy with respect to ORR per RECIST 1.1 by BICR. Hypothesis (H4): Pembrolizumab + lenvatinib results in a superior ORR per RECIST 1.1 based on BICR, compared with lenvatinib monotherapy.	Objective response, defined as a confirmed complete response (CR) or partial response (PR).

To assess DOR with pembrolizumab + lenvatinib and docetaxel per RECIST 1.1 by BICR.	DOR, defined as the time from the first documented evidence of CR or PR until PD or death due to any cause, whichever occurs first, in participants demonstrating CR or PR.
To assess the safety and tolerability of treatment with pembrolizumab + lenvatinib versus docetaxel. To assess the safety and tolerability of treatment with lenvatinib monotherapy.	Adverse events (AEs) and discontinuations due to AEs.
To compare pembrolizumab + lenvatinib to docetaxel with respect to the mean change from baseline in global health status/quality of life (QoL), cough, chest pain, dyspnea, and physical functioning.	Scores for the following scales/items: Global health status/QoL (European Organization for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire Core 30 items [QLQ-C30] Items 29 and 30) Cough (EORTC Quality of Life Questionnaire Lung Cancer Module 13 [QLQ-LC13] Item 31) Chest pain (EORTC QLQ-LC13 Item 40) Dyspnea (EORTC QLQ-C30 Item 8) Physical functioning (EORTC QLQ-C30 Items 1 to 5)
To compare pembrolizumab + lenvatinib to docetaxel with respect to time to true deterioration (TTD) in global health status/QoL, cough, chest pain, dyspnea, and physical functioning scales.	TTD, defined as the time from baseline to the first onset of ≥10-point decrease from baseline, with confirmation by the subsequent visit of ≥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) Physical functioning (EORTC QLQ-C30 Items 1 to 5)
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
To assess DCR12 with pembrolizumab + lenvatinib per RECIST 1.1 by BICR.	Disease control at 12 weeks, defined as CR, PR, or stable disease (SD) at 12 weeks.

To assess ORR with lenvatinib monotherapy versus docetaxel per RECIST 1.1 by BICR.	Objective response, defined as a confirmed complete response (CR) or partial response (PR).
To assess OS and PFS with pembrolizumab + lenvatinib versus lenvatinib monotherapy, and lenvatinib monotherapy versus docetaxel per RECIST 1.1 by BICR.	OS, defined as the time from randomization to the date of death due to any cause. PFS, defined as the time from randomization to the first documented progressive disease (PD) or death due to any cause, whichever occurs first.
To evaluate and compare participants' health status as assessed using the European Quality of Life 5-Dimension 5-Level (EuroQoL EQ-5D-5L) questionnaire, to generate utility scores for use in economic models (pembrolizumab + lenvatinib versus docetaxel).	Health utilities, assessed using the EuroQoL EQ-5D-5L.
Objective: To assess the pharmacokinetics (PK) of lenvatinib when coadministered with pembrolizumab.	Plasma concentration of lenvatinib versus time.
Objective: 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/or lenvatinib and/or docetaxel.	Genomic, metabolic, 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 randomized, open-label, multi-site, active-controlled study of pembrolizumab + lenvatinib versus docetaxel. The efficacy of lenvatinib (24 mg QD) will also be compared to both pembrolizumab + lenvatinib and docetaxel. Participants with metastatic NSCLC and PD after platinum doublet chemotherapy and treatment with one prior anti-PD-1/PDL1 mAb (either sequentially or in combination with chemotherapy) will be enrolled in the study. Staging for metastatic NSCLC will be based on the American Joint Committee on Cancer (AJCC) Staging Manual, version 8 or current version. This study will be conducted in participants with measurable disease and in whom *EGFR*-, *ALK*-, or *ROS1*-targeted therapy is not indicated.

Participants will provide archival tumor tissue obtained any time from initial diagnosis of NSCLC and prior to receiving immunotherapy (anti-PD-1/PD-L1) for determination of PD-L1 expression and study stratification. Participants will be stratified by:

- Anti-PD-1/PD-L1 mAb (immediate prior therapy versus not the immediate prior therapy)
- PD-L1 TPS (<50% versus ≥50%)
- ECOG performance status (0 versus 1)

Additionally, a newly obtained tumor tissue biopsy, obtained after immunotherapy (anti-PD-1/PD-L1) and before randomization is required. No systemic anticancer therapy may be administered between the biopsy and initiation of study treatment intervention.

Participants will also provide prestudy imaging scans to a CIV to confirm that they are of acceptable diagnostic quality to document PD before randomization. The site's study team must have reviewed and submitted images that are of diagnostic quality from at least 2 dates, to determine that radiographic progression has occurred per RECIST 1.1 within 12 weeks (84 days) of the last dose of treatment with an anti-PD-1/PD-L1 mAb. The central vendor will not be confirming eligibility before randomization.

Initial Treatment

Participants will be randomized 4:4:1 to:

- Pembrolizumab + lenvatinib (Arm 1)
- Docetaxel (Arm 2)
- Lenvatinib monotherapy (Arm 3)

All participants will receive a randomization number.

No treatment crossover is planned for the study.

Overall, approximately 405 participants will be randomized, including 180 participants each in Arm 1 and Arm 2, and approximately 45 participants in Arm 3.

The study design is shown in Figure 1 (Initial Treatment) and Figure 2 (Second Course).

A single-arm futility analysis will be conducted after 18 participants have been randomized to pembrolizumab + lenvatinib (Arm 1) and have been followed up for 20 weeks.

Futility rules are specified in Section 9.7.2.

Participants will be evaluated with radiographic imaging to assess response to study intervention every 6 weeks from randomization through 36 weeks, every 9 weeks through 54 weeks, and subsequently every 12 weeks until confirmed PD or initiation of a new anticancer regimen. All imaging obtained during the study will be submitted to the CIV for BICR, which will assess the images using RECIST 1.1 (Section 4.2.1.1.2) for determination of PFS and ORR. The tumor imaging showing site-assessed PD should be submitted immediately for verification by BICR before study intervention discontinuation. Treatment-based decisions may use site-assessed iRECIST as described in Section 8.2.1.7, which allows participants with initial site-assessed PD to continue study intervention until PD is confirmed by the site 4 to 8 weeks later.

Survival follow-up will continue after PD, discontinuation of study intervention, and the start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the study.

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

Treatment with pembrolizumab will continue for up to 35 treatment cycles, or until a discontinuation criterion is met (see Section 7.1). Treatment with pembrolizumab may be discontinued for participants with a confirmed CR who have received at least 6 months (8 cycles) of pembrolizumab.

Treatment with docetaxel may continue until a discontinuation criterion (see Section 7.1) is met.

Treatment with lenvatinib may continue until a discontinuation criterion (see Section 7.1) is met.

Participants receiving pembrolizumab will be permitted to continue study treatment beyond RECIST 1.1-defined PD, as long as the treating investigator considers that the participant may experience clinical benefit with continued treatment per iRECIST, and the participant is clinically stable and tolerating study intervention, until PD is confirmed by iRECIST. All decisions to continue treatment beyond confirmed PD by iRECIST must be approved by the Sponsor.

Second Course

Participants who stop pembrolizumab after receiving 35 treatment cycles of pembrolizumab or participants who stop study intervention after attaining a confirmed CR may be eligible for up to 17 additional treatment cycles of pembrolizumab upon experiencing BICR-verified PD. This retreatment is termed the Second Course and is only available if the study remains open and the participant meets the criteria in Section 8.10.3. The decision of whether to continue lenvatinib during the Second Course will be at the discretion of the investigator, unless lenvatinib was discontinued due to a toxicity. If continued, participants will be retreated at the same dose and frequency as when they last received the combination of pembrolizumab and lenvatinib. Radiographic imaging to assess response to study intervention will be performed every 12 weeks.

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

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

This study is being conducted to evaluate the efficacy and safety of pembrolizumab + lenvatinib in metastatic NSCLC. Lenvatinib (20 mg QD) will be evaluated in combination with the standard dose of pembrolizumab (200 mg Q3W). The study is open-label because of different infusion times for each treatment and predosing medication in the docetaxel arm. If the safety profile is acceptable and this combination improves outcomes, the study could support the regulatory approval of pembrolizumab + lenvatinib in patients with metastatic NSCLC previously exposed to an anti-PD-1/PD-L1 mAb. The efficacy and safety of lenvatinib monotherapy will be evaluated.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

4.2.1.1.1 Primary Efficacy Endpoints

This study has dual primary endpoints: OS and PFS.

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

PFS is an acceptable measure of clinical benefit for a late-stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable benefit/risk profile. The use of BICR and RECIST 1.1 to assess PFS is typically considered acceptable by regulatory authorities. Images will be read by a CIV blinded to study intervention assignment to minimize bias in response assessments. In addition, the final determination of radiologic progression will be based on the central

assessment of progression, rather than on a local site assessment. The CIV will verify progression by RECIST 1.1 in real time.

4.2.1.1.2 Secondary Efficacy Endpoints

In an exploratory analysis in patients with metastatic NSCLC treated with a PD-1 inhibitor, there was a correlation between objective response and OS; therefore, objective response and DOR per RECIST 1.1 as assessed by BICR are considered preliminary evidence of efficacy. As ancillary markers of efficacy, they are also chosen to be secondary endpoints in the study.

Additional secondary endpoints in this study include safety endpoints and patient-reported outcomes (PROs) (Sections 4.2.1.2. and 4.2.1.3).

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

For details of assessing efficacy endpoints using RECIST 1.1, see Appendix 8.

4.2.1.2 Safety Endpoints

Safety parameters frequently used for evaluating investigational-systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs, and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, Version 4.0.

4.2.1.3 Rationale for Patient-reported Outcomes

Symptomatic improvement is considered a clinical benefit and is accepted by health authorities. As part of the analyses for this study, participants will provide information regarding their health-related QoL via the EORTC QLQ-C30, EORTC QLQ-LC13, and EuroQoL-5D-5L (EQ-5D-5L) 5L questionnaires. The EORTC QLQ-C30 and EQ-5D-5L PROs are not pure efficacy or safety endpoints because they are affected by both PD and treatment tolerability.

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

4.2.1.3.1 EORTC QLQ-C30

EORTC QLQ-C30 is the most widely used cancer-specific health-related 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), and 6 single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and includes a global health and QoL scale [Aaronson, N. K., et al 1993]. 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

EORTC QLQ-LC13, a supplemental lung cancer-specific module used in combination with QLQ-C30, comprises 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, 4 = very much) and has been translated and validated into more than 60 languages.

4.2.1.3.3 EuroQoL-5D-5L (EQ-5D-5L)

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

4.2.1.4 Exploratory Endpoints

4.2.1.4.1 Disease Control at Week 12

The exploratory endpoint, disease control at Week 12 per RECIST 1.1 as assessed by BICR, will be used in the futility analysis as well as objective response. It is considered as a preliminary evidence of efficacy at an earlier stage of the study.

4.2.1.4.2 Pharmacokinetic Endpoints

Standard PK parameters of clearance and volume of distribution at steady state are planned to be calculated for lenvatinib in this study, using the accepted mixed-effects modeling approach. PK data 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 participant population.

PK evaluations will be performed for the first 90 participants in Arm 1.

4.2.1.4.3 Health Utilities

The EQ-5D-5L, and data for developing health utilities, are described in Section 4.2.1.3.3.

4.2.1.4.4 Genomic, Metabolic, or Proteomic Determinants of Response or Resistance to Treatments

Genomic, metabolic, and proteomic determinants of response or resistance to treatments are described in Section 4.2.1.5.

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- or and growth factor related signaling pathways related to pembrolizumab and lenvatinib 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 cancer, 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.

Genomic, metabolic, or proteomic determinants of response or resistance to treatment will be identified, and exploratory biomarker research will be conducted.

4.2.2 Rationale for Use of Comparator

Docetaxel is approved as 2L therapy for locally advanced or metastatic NSCLC after platinum therapy failure and is the most commonly prescribed 2L agent.

4.3 Justification for Dose

4.3.1 Lenvatinib

The dosing regimen for lenvatinib in combination with pembrolizumab was selected based on the results of Phase 1b/2 Study 111/KEYNOTE-146, whose primary endpoints were the MTD and RP2D of lenvatinib in combination with pembrolizumab 200 mg Q3W. Thirteen participants, including 3 receiving lenvatinib 24 mg/day + pembrolizumab 200 mg Q3W and 10 receiving lenvatinib 20 mg/day + pembrolizumab 200 mg Q3W, were enrolled in the Phase 1b study. Eight of these participants had RCC, 2 had NSCLC, 2 had endometrial cancer, and 1 had melanoma. There were 2 DLTs at the dose of lenvatinib 24 mg/day + pembrolizumab 200 mg Q3W; 1 participant had Grade 3 arthralgia, and another had Grade 3 fatigue. Accordingly, this dose was defined as the toxic dose. No DLTs were reported in the10 participants who received lenvatinib 20 mg/day + pembrolizumab 200 mg Q3W. All participants experienced at least 1 treatment-emergent AE (TEAE). TEAEs necessitating dose modification included increased liver function tests (LFTs), fatigue, hypertension, arthralgia, decreased appetite, dehydration, diarrhea, hyponatremia, noncardiac chest pain, palmar-plantar erythrodysesthesia, proteinuria, maculopapular rash, and rhabdomyolysis. Based on review of all clinical data from these 13 participants, the MTD and RP2D were determined to be 20 mg lenvatinib QD with a fixed dose of 200 mg pembrolizumab Q3W. Based on the promising antitumor efficacy and tolerable safety profile in both the endometrial cancer and RCC expansion cohorts in Study 111/KEYNOTE-146 [Makker, V., et al 2018], 2 Phase 3 studies have been initiated for both of these tumor types: Study E7080-G000-309/KEYNOTE-775 and Study E7080-G000-307/KEYNOTE-581.

The safety and efficacy of the combination of pembrolizumab and lenvatinib at the lenvatinib RP2D is being assessed in the Phase 2 portion of this study that includes 6 cohorts (NSCLC, RCC, endometrial cancer, urothelial carcinoma, melanoma, and squamous cell carcinoma of the head and neck).

The dose selected for the lenvatinib monotherapy arm, 24 mg QD, is based on Study E7080-703, and is the recommended dose in locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer.

4.3.2 Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg Q3W. The rationale for use of a fixed pembrolizumab dose in participants with solid tumors was based on:

- Similar efficacy and safety of pembrolizumab at doses of 2 mg/kg Q3W, 10 mg/kg Q3W, or 10 mg/kg every 2 weeks (Q2W) in participants with melanoma and NSCLC.

- Flat exposure-response relationships for pembrolizumab for both efficacy and safety in the dose range of 2 mg/kg Q3W to 10 mg/kg Q3W.

- Lack of clinically relevant effect of tumor burden or indication on distribution behavior of pembrolizumab, as assessed by the population pharmacokinetics (PopPK) model.

- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically-based PK analysis) at 200 mg Q3W.

The choice of 200 mg Q3W pembrolizumab as an appropriate fixed dose was based on simulations using the PopPK model of pembrolizumab, showing that a fixed dose of 200 mg Q3W would:

- Provide similar control of PK variability as does weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and the 2 mg/kg Q3W dose.

- Maintain individual participant exposures in the exposure range associated with maximal efficacy response established in participants with melanoma and NSCLC.

- Result in individual participant exposures within a range that was well tolerated and safe in participants with melanoma and NSCLC.

Clinical data have shown meaningful improvement in benefit/risk relationship, including OS at 200 mg Q3W across multiple indications. Additionally, a fixed dose regimen simplified dosing, to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme also reduced complexity in the logistic chain at treatment facilities and reduced wastage.

4.3.3 Maximum Dose Exposure for This Study

The maximum dose/exposure of pembrolizumab allowed in this study is 200 mg IV Q3W for up to 2 years (35 treatment cycles) of initial treatment (Section 8.10.2), and for up to 1 year (17 treatment cycles) of Second Course treatment (Section 8.10.3). The maximum dose of lenvatinib is 20 mg PO QD in Arm 1 and 24 mg PO QD in Arm 3. The maximum dose of docetaxel is 75 mg/m^2 IV. Lenvatinib and docetaxel may be continued until a discontinuation criterion (eg, PD) is met (Section 7.1).

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative [Appendix 7, Section 10.7.1]) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

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

4.4.1 Clinical Criteria for Early Study Termination

The prespecified stopping rules are detailed in Section 9.7.2.

In addition, the study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio for the study population as a whole is unacceptable. Moreover, 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 or female participants with metastatic NSCLC and PD after platinum doublet chemotherapy and an anti-PD-1/PD-L1 mAb (either concomitantly or sequentially) who are at least 18 years of age may be enrolled into the study.

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

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

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Have a histologically or cytologically confirmed diagnosis of metastatic squamous or nonsquamous NSCLC (Stage IV: M1a, M1b, M1c, AJCC Staging Manual, version 8).

   Note: Mixed tumors will be characterized by the predominant cell type. If small cell elements are present, the participant is ineligible.
2. Have PD on treatment with <u>one</u> prior anti-PD-1/PD-L1 mAb administered either as monotherapy or in combination with other checkpoint inhibitors or other therapies. Anti-PD-1/PD-L1 treatment progression is defined by meeting ALL of the following criteria:

   Treatment with at least 2 doses of an anti-PD-1/PD-L1 mAb.

   PD after an anti-PD-1/PD-L1 mAb as defined by RECIST v1.1: Evidence of PD is defined as:

   1) imaging prior to anti-PD-1/PD-L1 treatment or image showing nadir during anti-PD-1/PD-L1 treatment; AND

   2) imaging to determine that radiographic progression has occurred per RECIST 1.1 within 12 weeks (84 days) from the last dose of an anti-PD-1/PD-L1 mAb.

   Note: Retreatment with the <u>same</u> anti-PD-L1/PD-L1 mAb is acceptable in the overall course of treatment.

   Note: The CIV must have received these scans and have confirmed with the site that the images are of acceptable diagnostic quality prior to treatment allocation in this study. The CIV will not be confirming disease progression prior to treatment allocation. The image

showing progression may be the baseline tumor image for the trial, if collected during the 30-day screening window.

3. Have PD during/after platinum doublet chemotherapy for metastatic disease.

   Note: A platinum-containing doublet is defined as a platinum-based cytotoxic systemic agent administered in the same cycle as another cytotoxic systemic chemotherapeutic agent.

   Note: Completion of treatment with a platinum-containing doublet as neo-adjuvant or adjuvant therapy or as part of definitive chemo-radiation treatment for early stage disease (Stage I-III) within 1 year of providing documented informed consent will satisfy the prior platinum doublet chemotherapy treatment requirement.

   Note: Eligible participants will have PD after an anti-PD-1/PD-L1 therapy AND platinum doublet chemotherapy (sequentially or concomitantly). The prestudy images submitted to the CIV will be images of PD on treatment with an anti-PD-1/PD-L1 mAb, and NOT images associated with PD on platinum doublet chemotherapy given sequentially.

4. Have confirmation that *EGFR*-, *ALK*-, or *ROS1*-directed therapy is not indicated as primary therapy (documentation of absence of tumor-activating *EGFR* mutations [eg, *DEL19* or *L858R*], and absence of *ALK* and *ROS1* gene rearrangements OR presence of a K-*ras* mutation).

   Note: If the participant's tumor is known to have a predominantly squamous histology, molecular testing for *EGFR* mutations and *ALK* and *ROS1* translocations will not be required, as this testing is not part of current diagnostic guidelines.

   Note: Participants who have failed directed therapy are not eligible for the study.

5. Have submitted prestudy imaging that confirmed evidence of PD based on investigator review of at least 2 images per RECIST 1.1, following initiation of an anti-PD-1/PD-L1 mAb.

   Note: These images will be submitted to the CIV for confirmation that they are of acceptable diagnostic quality. The CIV must have received these images and confirmed that they are of acceptable diagnostic quality before randomization.

6. Have measurable disease based on RECIST 1.1 as determined by the local site assessment.

   Have at least 1 measurable lesion by CT or MRI per RECIST 1.1.

   Note: Lesions that appear measurable but are 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 radiation.

7. Have provided tumor tissue for PD-L1 biomarker analysis from an archival sample (defined as: from initial diagnosis of NSCLC and prior to receiving immunotherapy [anti-PD-1/PD-L1], from the primary lesion or a metastatic lesion).

   Note: The tissue sample must be received and evaluated by the central vendor before randomization for stratification in the study. Formalin-fixed, paraffin-embedded (FFPE) tissue blocks are preferred to slides. Fine-needle aspirates are not acceptable.

   Note: As of 16-JUN-2021, the archival tissue sample and evaluation may be from a previous MSD study that the subject was enrolled in (ie, MK-3475-024, -042, -189, -407, -654, and -715) where the sample was evaluated by the same central laboratory.

8. Have provided prior to randomization tissue from a newly obtained formalin-fixed sample from a new biopsy (defined as: after completion of immunotherapy [anti-PD-1/PD-L1] and before receiving a randomization number) of a tumor lesion not previously irradiated.

   Note: **No systemic anticancer therapy may be administered between the newly obtained PD-L1 biopsy and initiation of study intervention.** The tissue sample must be shipped to the central vendor before randomization. FFPE tissue blocks are preferred to slides. Fine-needle aspirates are not acceptable.

   Note: For participants from whom obtaining a new tumor biopsy would be medically inappropriate, the investigator may request an exception from the Sponsor's study clinical director. If there is agreement, a waiver will be granted.

Demographics

9. Be ≥18 years of age on the day of providing documented informed consent.
10. Have ECOG performance status of 0 or 1 within 7 days before the first dose of study intervention but before randomization.

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

Male Participants

12. Male participants receiving pembrolizumab ± lenvatinib or lenvatinib are eligible to participate if they agree to the following during the intervention period or 7 days after the last dose of lenvatinib:

    Male participants randomized to docetaxel are eligible to participate if they agree to the following during the intervention period and for at least 90 days after the last dose of docetaxel:

    - 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.

  - 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 are more stringent than the requirements above, the local label requirements are to be followed.

Note: Upon 7 days after lenvatinib is stopped, if the participant is on pembrolizumab only, no male contraception measures are needed.

Female Participants

13. A female participant is eligible to participate if she is not pregnant or breastfeeding and at least 1 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 is abstinent from heterosexual intercourse as her 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 after the last dose of pembrolizumab or 30 days after the last dose of lenvatinib, whichever occurs last; and agrees not to donate eggs (ova, oocytes) to others or freeze/store these for her own use for the purpose of reproduction during this period. 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 randomized to docetaxel is eligible to participate if she is using a contraceptive method that is highly effective with low user dependency or is abstinent from heterosexual intercourse as her preferred and usual lifestyle and agrees not to donate or freeze/store eggs during the intervention period and for at least 30 days after the last dose of docetaxel.

- A WOCBP must have a negative highly sensitive pregnancy test ([urine or serum] as required by local regulations [see Appendix 7]) within 24 hours for urine or within 72 hours for serum before the first dose of study intervention.

- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

- Additional requirements for pregnancy testing during and after study intervention are in Appendix 2.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk of inclusion of a woman with an early undetected pregnancy.

- Contraceptive use by females 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 are more stringent than the requirement above, the local label requirements are to be followed.

Informed Consent

14. Have provided (or legally acceptable representative [see Appendix 7, Section 10.7.1]) documented informed consent for the study.

Medical History and Laboratory Values

15. 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 before randomization.

    Note: Participants must not have a history of uncontrolled or poorly controlled hypertension, defined as ≥150/90 mm Hg for >4 weeks despite standard medical management.

16. If participant received major surgery or radiation therapy of >30 Gy, they have recovered from the toxicity and/or complications from the intervention.
17. Have adequate organ function as defined in Table 1. Specimens must be collected within 10 days before the start of study intervention.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematologic	
Absolute neutrophil count	≥1500/μL
Platelets	≥100,000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine or measured or calculated[b] CrCl (GFR can be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participants with creatinine >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 × ULN OR direct bilirubin ≤ULN for participants with total bilirubin >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
INR or PT aPTT	≤1.5 × ULN unless the participant is receiving anticoagulants, as long as PT or aPTT is within the therapeutic range for intended use of anticoagulants

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

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations (see Appendix 7) and guidelines for administration of specific chemotherapies.

[a] This criterion must be met without erythropoietin dependency and without packed red blood cell transfusion within the last 2 weeks.

[b] CrCl should be calculated per the institutional standard.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

Prior/Concomitant Therapy

1. Has received docetaxel as monotherapy or in combination with other therapies.
2. Has received lenvatinib as monotherapy or in combination with an anti-PD-1/PD-L1 mAb.
3. Has received radiotherapy within 2 weeks before the first dose of study intervention or has received lung radiation therapy >30 Gy within 6 months before the first dose of study intervention.

   Note: Participants must have recovered to Grade 1 or less from all radiation-related toxicities, must not require corticosteroids, and must not have had radiation pneumonitis.

4. Has received a live vaccine within 30 days before the first dose of study intervention.

   Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

Medical Conditions

5. Has clinically significant hemoptysis (at least 0.5 teaspoon of bright red blood) or tumor bleeding within 2 weeks before the first dose of study intervention.
6. Has radiographic evidence of intratumoral cavitation, 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.
7. Has clinically significant cardiovascular impairment within 12 months of the first dose of study intervention, such as history of congestive heart failure greater than New York Heart Association Class II, unstable angina, myocardial infarction or cerebrovascular accident/transient ischemic attack (TIA)/stroke, cardiac revascularization, or cardiac arrhythmia associated with hemodynamic instability.

   Note: Medically controlled arrhythmia that is stable with medication is permitted.

8. Has a history of a gastrointestinal condition or procedure that, in the opinion of the investigator, may affect oral study intervention absorption.
9. Has a pre-existing ≥Grade 3 gastrointestinal or non-gastrointestinal fistula.
10. Is a WOCBP who has a positive urine pregnancy test within 24 hours or a positive serum pregnancy test within 72 hours before randomization (see Appendix 5).

    Note: If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. If 24 hours have elapsed between the screening urine (or 72 hours for a screening serum pregnancy test) and the first dose of study intervention, another pregnancy test (urine or serum) must be performed and must be negative for the participant to start receiving study intervention.

Prior/Concurrent Clinical Study Experience

11. Is currently participating in a clinical trial and receiving study therapy or participated in a study of an investigational agent within 4 weeks of the first dose of study intervention.

    Note: Participants who have entered the survival follow-up phase (due to PD) in an investigational study with a PD-1/PD-L1 inhibitor may participate in this study if it has been >4 weeks since the last dose of treatment and the participant meets the entry criteria for the study.

    Note: The 4-week window should also be applied to the last dose of antineoplastic investigational agent or last use of an investigational device with antineoplastic intent.

Note: Participants must have resolution of toxic effect(s) of the most recent therapy (eg, chemotherapy) to Grade 1 or less (except alopecia). If participants underwent major surgery within 3 weeks prior to the first dose of study intervention, they must have recovered from any toxicity and/or complications from the intervention. Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility.

Diagnostic Assessments

12. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (exceeding 10 mg of prednisone or equivalent daily) or any other form of immunosuppressive therapy within 7 days before the first dose of study intervention.
13. Has a known history of an additional malignancy, except if the participant has undergone potentially curative therapy with no evidence of disease recurrence for 3 years since initiation of that therapy.

    Note: The requirement for no evidence of disease for 3 years does not apply to the NSCLC for which a participant is enrolled in the study. This 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.

14. Has known active central nervous system metastases and/or carcinomatous meningitis.

    Note: Participants with previously treated brain metastases may be enrolled in the study provided they are radiologically stable (ie, without evidence of progression for at least 4 weeks by repeat imaging [repeat imaging should be performed during study screening]), are clinically stable, and are without requirement for steroid treatment for at least 14 days before the first dose of study intervention.

15. Has severe hypersensitivity (Grade ≥3) to pembrolizumab and/or any of its excipients.
16. Has a sensitivity to any of the excipients contained in lenvatinib.
17. Has a sensitivity to any of the excipients contained in docetaxel.
18. 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).

    Note: Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

19. Has a history of (noninfectious) pneumonitis that required systemic steroids or current pneumonitis/interstitial lung disease.
20. Has an active infection requiring systemic therapy.
21. Has a known history of human immunodeficiency virus (HIV) infection.

    Note: No HIV testing is required unless mandated by the local health authority (see Appendix 7).

22. Has a known history of hepatitis B (defined as hepatitis B surface antigen [HbsAg]) reactive or known active hepatitis C virus (HCV) (defined as HCV RNA [qualitative] is detected) infection.

    Note: No testing for hepatitis B and hepatitis C is required unless mandated by the local health authority (see Appendix 7).

23. Has active tuberculosis.
24. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study or interfere with the participant's participation for the full duration of the study, or it is not in the best interest of the participant to participate, in the opinion of the treating investigator.
25. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.
26. Has a left ventricular ejection fraction (LVEF) below the institutional normal range, as determined by multigated acquisition (MUGA) or echocardiogram (ECHO).
27. Has QT interval corrected with Fridericia's formula (QTcF) prolongation to >480 ms.
28. Participants with proteinuria ≥2+ (≥100 mg/dL) on urine dipstick testing/urinalysis will undergo 24-hour urine collection for quantitative assessment of proteinuria. Participants with urine protein ≥1 g/24 h will be ineligible.

Other Exclusions

29. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through at least 120 days after the last dose of pembrolizumab or lenvatinib, or 90 days (for male participants) and 30 days (for female participants) after the last dose of docetaxel.

    Note: If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.
30. Has had an allogeneic tissue/solid organ transplant.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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

5.3.2 Pregnancy

If a participant inadvertently becomes pregnant while receiving study intervention, she will be immediately discontinued from study intervention. The site will contact the participant at least monthly and document her 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 in 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 a 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 in Section 8.4.5.

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 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 (pembrolizumab, lenvatinib, and docetaxel) will be packaged to support enrollment as required. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 2.

Note: In alignment with the study-specific investigator letter dated 22-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 or docetaxel can continue treatment per investigator's discretion. Participants who are potential candidates for Second Course treatment will continue in Efficacy Follow-up.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1	Experimental	Pembrolizumab	Drug	Solution	25 mg/mL	200 mg	IV Infusion	Q3W	Test Product	IMP	Central
Arm 1	Experimental	Lenvatinib	Drug	Capsule	10 mg 4 mg	20 mg	Oral	QD	Test Product	IMP	Central
Arm 2	Active Comparator	Docetaxel	Drug	Solution	20 mg/ mL	75 mg/m^2	IV Infusion	Q3W	Comparator	IMP	Provided centrally by the Sponsor or locally by the study site, sub-sidearm, or designee
Arm 3	Experimental	Lenvatinib	Drug	Capsule	10 mg 4 mg	24 mg	Oral	QD	Test Product	IMP	Central

EEA=European Economic Area; IMP=investigational medicinal product; IV=intravenous; NA=not applicable; NIMP/AxMP=noninvestigational/auxiliary medicinal product; Q3W=every 3 weeks; QD=once daily.
The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

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

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

6.1.1 Medical Devices

Not applicable.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details of the preparation, storage, and administration of pembrolizumab are provided in the Pharmacy Manual.

Lenvatinib is provided as capsules for oral administration and does not require preparation. **If a lenvatinib dose is missed and cannot be taken within 12 hours of the scheduled dosing time, the participant should skip this dose and take the next dose at the scheduled time the next day.**

Docetaxel will be prepared and administered as per the approved local product label. Docetaxel 75 mg/m^2 will be administered as an IV infusion over 1 hour Q3W. All participants randomized to docetaxel should be premedicated with oral or injectable steroids for 3 days starting 1 day prior to docetaxel administration to reduce the risk of fluid retention and the severity of hypersensitivity reactions (or according to the approved product label). Additional premedications may be administered as per standard practice.

See the Pharmacy Manual for additional information.

The rationale for selection of doses to be used in this study is in Section 4.3.

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 IRT system. There are 3 study intervention arms. Participants will be assigned randomly in a 4:4:1 ratio to the pembrolizumab + lenvatinib arm, docetaxel arm, or the lenvatinib monotherapy arm, they will receive a randomization number.

6.4 Stratification

Stratification factors are as follows:

- Anti-PD-1/PD-L1 mAb (immediate prior therapy versus not the immediate prior therapy)
- PD-L1 TPS (<50% versus ≥50%)
- ECOG performance status (0 versus 1)

6.4.1 Blinding

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

Although the trial is an open-label study, with analyses or summaries generated by study intervention assignment, access to the information on actual study intervention received will be limited and documented.

The treatment-level results of the interim analyses will not be shared with the investigator before completion of the study.

6.4.1.1 TPS Results

Individual PD-L1 status will not be disclosed to the sites and study participants. Analyses by PD-L1 biomarker status will be limited and documented.

If TPS score is nonevaluable, the participant will be stratified into the <50% group.

6.5 Study Intervention Compliance

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

6.6 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 that is specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor. 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.

Medication considered necessary for the participant's health and not expected to interfere with the evaluation of or interact with the study intervention may be continued during the study. Palliative and supportive care is permitted during the study for underlying medical conditions and symptom management. Surgery or radiotherapy for tumor control is not permitted during the study.

All prior and concomitant medications (including over-the-counter medications) received within 30 days before the first dose of study intervention and during the course of the study (starting at the date of documented informed consent) until 30 days after the last dose of study intervention at the Safety Follow-up visit (or 90 days after the last dose of study intervention if used to treat an SAE) should be recorded on the appropriate electronic case report form (eCRF). The investigator will record the AE for which the concomitant medication/therapy was administered on the appropriate eCRF. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the appropriate eCRF. After the Safety Follow-up visit, record all medications taken for SAEs and events of clinical interest (ECIs) as defined in Section 10.3.

> **Note: Information on all prior anticancer agents will be collected and recorded on the eCRF during the Screening Visit (eg, 1L, 2L, 3L, etc.).**

If a participant enters the Second Course, all concomitant medications received within 30 days before the first dose of Second Course treatment should be recorded. After the Second Course Safety Follow-up visit, record all medications received for SAEs and ECIs as defined in Section 10.3.

Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded.

6.6.1 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 intervention. Anti-emetic or any other prophylaxis should be considered in accordance with institutional guidelines.

The following concomitant medications are also allowed:

- Premedication and postmedication for docetaxel administration
- Hormone replacement therapy
- Thyroid hormone suppressive therapy
- Anticoagulants, including low molecular weight heparin, warfarin, anti-Xa agents
- Anti-inflammatory agents
- Bisphosphonates or denosumab
- Antihypertensive therapy (including additional antihypertensive treatment as appropriate if BP increases once the participant is enrolled)

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

6.6.2 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 tumor debulking, 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 vaccines within 30 days before the first dose of study intervention and while participating in the study (see exclusion criterion 4 for examples).

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an immune-related AE (Section 6.6.3.1), as premedication or postmedication for docetaxel, as premedication before CT scanning in participants with contrast allergy, or for exacerbations of chronic obstructive pulmonary disease requiring steroids for recovery. Replacement doses of steroids (eg, prednisone 10 mg daily) are permitted during the study. **Note:** Inhaled steroids are allowed for management of asthma or seasonal allergies. See Section 6.5.4.1 for additional information.

- 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.

For participants who, in an assessment by the investigator, require the use of any of the aforementioned treatments for clinical management, continuation of study intervention 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 PD, and study intervention will be discontinued. These participants should complete all end of treatment assessments and continue to be followed for survival in the follow-up period.

6.6.3 Drug Interactions

There are no DDI-related concomitant medication prohibitions or restrictions.

Lenvatinib is not expected to produce a clinically meaningful alteration in exposure to CYP3A4/ P-glycoprotein (Pgp) substrates based on results from a lenvatinib drug-drug interaction (DDI) study with midazolam (a sensitive CYP3A and Pgp substrate).

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

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

6.6.4 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator.

For participants receiving pembrolizumab plus lenvatinib, suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined in Table 4 in Section 6.6.3.1 along with the dose modification guidelines in Table 3 in Section 6.6.2.

Where appropriate, these guidelines include the use of oral or IV corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary, as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab or lenvatinib.

> **Note:** If, after the 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. Refer to Table 3 for guidelines regarding dose modification and supportive care.

Participants in the docetaxel arm should receive premedication with corticosteroids for 3 days before docetaxel administration to reduce the risk of fluid retention and the severity of hypersensitivity reactions.

Refer to the approved product label for docetaxel dose interruptions and dose reductions.

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

6.6.4.1 Systemic Corticosteroid Use

Systemic corticosteroids are permitted in the following situations:

- For treatment of potential immune-related adverse events (irAEs), as indicated in Table 4.
- As premedication for docetaxel administration.
- As pre- or postmedication to prevent AEs associated with IV contrast material.
- As considered necessary for a participant's medical condition.
- Brief, limited use (≤7 days) of systemic corticosteroids is permitted when considered SOC (eg, for exacerbation of chronic obstructive pulmonary disease).

Replacement doses of steroids (eg, prednisone 10 mg daily) are permitted during the study, as are local steroid injections and topical steroids.

6.7 Dose Modification (Escalation/Titration/Other)

6.7.1 Concomitant Combination Therapy

If either pembrolizumab is interrupted for >12 weeks (irAE) or >3 weeks (administrative reasons) or lenvatinib is interrupted for 28 consecutive days, the site must gain approval from the Sponsor prior to restarting treatment. Participants who must interrupt or discontinue 1

drug in the combination due to drug-related AEs may continue with the other drug in the combination until criteria for treatment discontinuation are met (eg, PD).

6.7.2 Lenvatinib Dose Modification and Toxicity Management

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

AEs will be graded using NCI CTCAE, version 4.0. Investigators will decide the probability of events being related to 1 or both drugs to determine whether dose modification of 1 or both drugs is required.

The starting dose of lenvatinib is 20 mg/day for participants enrolled in the combination treatment arm (Arm 1). Lenvatinib dose reductions will take place in succession based on the previous dose level (14, 10, and 8 mg/day). Any dose reduction below 8 mg/day must be discussed with the Sponsor.

The starting dose of lenvatinib is 24 mg/day for participants enrolled in the monotherapy treatment arm (Arm 3). Lenvatinib dose reductions for Arm 3 will take place in succession based on the previous dose level (20, 14, and 10 mg/day). Any dose reduction below 10 mg/day must be discussed with the Sponsor.

For both Arm 1 and Arm 3, once the dose has been reduced, it may not be increased at a later date unless the dose has been mistakenly decreased; in this situation, the Sponsor's approval is required to increase the dose.

Refer to the sections below for management of hypertension (Section 6.6.2.1), proteinuria (Section 6.6.2.2), diarrhea (Section 6.6.2.3), hepatotoxicity (Section 6.6.2.4), thromboembolic events (Section 6.6.2.5), posterior reversible encephalopathy syndrome/ reversible posterior leukoencephalopathy syndrome (PRES/RPLS; Section 6.6.2.6), hypocalcemia (Section 6.6.2.7), hemorrhage (Section 6.6.2.8), gastrointestinal perforation or fistula formation (Section 6.6.2.9), QT prolongation (Section 6.6.2.10) and Osteonecrosis of the Jaw (Section 6.6.2.11) as appropriate, before consulting the dose modification table (Table 3). For overlapping toxicities of pembrolizumab and lenvatinib, refer to Section 6.6.4.

Table 3 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]		
First occurrence	Interrupt lenvatinib until resolved to Grade 0-1 or tolerable Grade 2	**Arm 1**: Reduce lenvatinib dose from 20 mg QD to 14 mg QD (1-level reduction) **Arm 3:** Reduce lenvatinib dose from 24 mg QD to 20 mg QD (1-level reduction)
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1 or tolerable Grade 2	**Arm 1:** Reduce lenvatinib dose from 14 mg QD to 10 mg QD (1-level reduction) **Arm 3:** Reduce lenvatinib dose from 20 mg QD to 14 mg QD (1-level reduction)
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1 or tolerable Grade 2	**Arm 1**: Reduce lenvatinib from 10 mg QD to 8 mg QD (1-level reduction) **Arm 3**: Reduce lenvatinib dose from 14 mg QD to 10 mg QD (1-level reduction)
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib	**Discuss with Sponsor**
Grade 3 AE of thromboembolic events **or Grade 4 AEs[f]:** Permanently **discontinue lenvatinib.**		

Abbreviations: AE = adverse event; BMI = body mass index; CTCAE = Common Terminology Criteria for Adverse Events; QD = once daily.
Note: For grading, see NCI CTCAE, version 4.0. Collect all AE grades (ie, decreasing and increasing NCI CTCAE grades).

a. An interruption of lenvatinib for more than 28 days will require the Sponsor's approval before lenvatinib can be resumed.
b. Initiate optimal medical management for nausea, vomiting, hypertension, hypothyroidism, and/or diarrhea before 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 10% of baseline weight (ie, Grade 1 weight loss). These participants will restart lenvatinib 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 lenvatinib should be discussed with the Sponsor.
f. Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

6.7.2.1 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 pembrolizumab + lenvatinib must have BP ≤150/90 mm Hg at the time of study entry and, if known to be hypertensive, have been taking a stable dose of antihypertensive medication for at least 1 week before C1D1. **Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions**.

BP should be regularly assessed as detailed in the SoA (Section 1.3). Hypertension will be graded using NCI CTCAE, version 4.0, based on BP measurements only, and not on the

number of antihypertensive medications. If the participant's initial BP is elevated (ie, systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), 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 (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements at least 5 minutes apart to yield a mean value.

Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg) is confirmed at 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 at 2 assessments at least 30 minutes apart. For participants already taking antihypertensive medication, treatment modification may be necessary if hypertension persists.

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

Participants who have had systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored on Day 15 of the current cycle (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 Day 15 evaluations until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles. Participants will have the option of having BP measurements between visits obtained locally by a health care professional. A diary will be provided as a tool to aid participants in collecting BP evaluations between study visits. The participant will bring the BP diary to the clinic at each visit; BP measurements will be recorded in the participant's chart and eCRF.

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

1. Continue lenvatinib and institute antihypertensive therapy for participants not already receiving this therapy.

2. For participants already taking antihypertensive medication, the dose of the current agent may be increased if appropriate, or 1 or more antihypertensive agents in a different class should be added. Study intervention can be continued without lenvatinib dose modification.

3. If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg persists despite maximal antihypertensive therapy, lenvatinib administration should be interrupted and restarted at 1 dose level reduction only when systolic BP is ≤150 mm Hg and diastolic BP is ≤95 mm Hg and the participant has been receiving a stable dose of antihypertensive medication for at least 48 hours.

    - If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg recurs at the first lenvatinib dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or addition of a different class of antihypertensive), lenvatinib 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 receiving a stable dose of antihypertensive medication for at least 48 hours.

    - If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg recurs at the second lenvatinib dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), lenvatinib 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 receiving 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 management of Grade 4 hypertension (life-threatening consequences):

a. Institute appropriate medical management.

b. Discontinue lenvatinib.

6.7.2.2 Management of Proteinuria

Proteinuria should be regularly assessed 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 or urinalysis testing per the SoA (Sections 1.3.1 and 1.3.3). Urine dipstick testing is the preferred method for testing for urinary protein, however, urinalysis may be used if the use of urine dipsticks is not feasible.

2. A 24-hour urine collection initiated as soon as possible and at least within 72 hours (or an immediate spot urine protein/creatinine ratio [UPCR] test) is required in the following situations:

    - The first (initial) occurrence of ≥2+ (≥100 mg/dL) proteinuria on urine dipstick testing or urinalysis while the participant is receiving lenvatinib.

- A subsequent increase in severity of proteinuria on urine dipstick testing or urinalysis at the same lenvatinib dose level.

- When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick or urinalysis result is ≥2+ (≥100 mg/dL).

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

Grading of Proteinuria

Grading according to NCI CTCAE, version 4.0, will be based on the 24-hour urinary protein result if available. If the participant has 4+ proteinuria by dipstick (≥1000 mg/dL by urinalysis), a 24-hour urinary protein result is required to confirm Grade 3 proteinuria. Management of lenvatinib administration will be based on the proteinuria grade according to Table 3.

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

Monitoring

Urine dipstick or urinalysis testing for participants with ≥2+ (≥100 mg/dL) proteinuria should be performed on Day 15 (or more frequently as clinically indicated) until results have been 1+ (30 mg/dL) or negative for 2 consecutive treatment cycles (see Section 8.3.5.1.2 for additional details).

Monitoring of proteinuria may be performed by the local laboratory or at the investigator site but must be managed by the site physician.

6.7.2.3 Management of Diarrhea

An antidiarrheal agent should be recommended to participants at the start of study intervention, and participants should be instructed and educated to initiate antidiarrheal treatment at the first onset of soft bowel movements. The choice of antidiarrheal agent should be individualized to the participant's clinical circumstances and should follow standard medical practice. If signs/symptoms of diarrhea persist despite optimal medical management, the instructions in Table 3 should be followed. For overlapping toxicities of pembrolizumab and lenvatinib, please refer to Section 6.6.4.

6.7.2.4 Management of Hepatotoxicity

LFTs (alanine aminotransferase [ALT], aspartate aminotransferase [AST], bilirubin) should be performed as detailed in the SoA (Section 1.3) and as clinically indicated. If signs/symptoms indicating liver injury occur, the instructions in Table 3 should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs, lenvatinib must be discontinued. Hepatic failure is defined as the CTCAE

definition. For overlapping toxicities of pembrolizumab and lenvatinib, please refer to Section 6.6.4.

6.7.2.5 Management of Thromboembolic Events

Participants should be advised to pay attention to symptoms suggestive of venous thromboembolic events, including acute onset of shortness of breath, dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, and deep vein thrombosis signs (lower extremity swelling and warmth to touch or tenderness). If any of these symptoms appear, participants should be instructed to report these symptoms promptly to the treating physician. If a thromboembolic event is confirmed, the instructions in Table 3 should be followed. Appropriate supportive care should be provided together with close monitoring.

If a Grade 3 thromboembolic AE occurs, lenvatinib will be permanently discontinued. If a participant experiences a life-threatening (Grade 4) thromboembolic event, including pulmonary embolism, lenvatinib must be discontinued. Arterial thromboembolic events (eg, new onset of, worsening, or unstable angina, myocardial infarction, TIA, and cerebrovascular accident) of any grade require study intervention discontinuation.

6.7.2.6 Management of PRES/RPLS

PRES/RPLS is a neurologic disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurologic 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, the instructions in Table 3 should be followed.

6.7.2.7 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 NCI CTCAE, version 4.0, using the following formula: corrected calcium = ([4 − serum albumin (g/dL)] × 0.8 + serum calcium). This formula is not applicable when serum albumin concentration is normal (>4 g/dL); if so, total (uncorrected) serum calcium should be used instead.

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

6.7.2.8 Management of Hemorrhage

The instructions in Table 3 should be followed for management of hemorrhage. Lenvatinib should either be resumed at a reduced dose or discontinued, depending on the severity and persistence of hemorrhage.

6.7.2.9 Management of Gastrointestinal Perforation or Fistula Formation

Permanently discontinue lenvatinib in any participant who develops gastrointestinal perforation of any grade or Grade 4 fistula.

6.7.2.10 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.

6.7.2.11 Management of Osteonecrosis of the Jaw

Perform an oral examination prior to treatment with lenvatinib and periodically during lenvatinib treatment. Advise participants regarding good oral hygiene practices. Avoid invasive dental procedures, if possible, while on lenvatinib treatment, particularly in participants at higher risk. For participants requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ. Withhold lenvatinib if ONJ develops and restart based on clinical judgment of adequate resolution (See Section 6.6.5).

6.7.3 Pembrolizumab

Pembrolizumab dose reductions are not permitted. Pembrolizumab may be interrupted or discontinued due to toxicity. Pembrolizumab may be interrupted for a maximum of 12 weeks (Section 6.4).

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

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

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

Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids.

Dose Modification and Toxicity Management Guidelines for irAEs Associated With Pembrolizumab Monotherapy, Coformulations, or IO Combinations are provided in Table 4.

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

General instructions:

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

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Recurrent Grade 2 or Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
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		
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

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
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]		
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		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
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).

6.7.3.2 Dose Modification and Toxicity Management for 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 for pembrolizumab-associated infusion reactions are provided in Table 5.

Table 5 Dose Modification and Treatment Guidelines for Pembrolizumab Infusion Reactions

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 h	**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 the drug infusion, the infusion may be restarted at 50% of the original rate (eg, from 100 mL/h to 50 mL/h). Otherwise, withhold dosing 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 pembrolizumab treatment.**	The participant may be premedicated 1.5 hours (± 30 minutes) before infusion of pembrolizumab with: - Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). - Acetaminophen 500 to 1000 mg PO (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 **Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms 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 case of anaphylaxis, epinephrine should be used immediately. **The participant is permanently discontinued from further pembrolizumab treatment.**	No subsequent dosing
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; NSAIDs = nonsteroidal anti-inflammatory drugs; PO = orally. Appropriate resuscitation equipment should be available at the bedside, and a physician should be readily available during drug administration. For further information, please refer to CTCAE, version 4.0, at http://ctep.cancer.gov		

6.7.4 Dose Modification 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 of lenvatinib treatment, while irAEs are risks of pembrolizumab treatment. However, certain AEs, such as diarrhea, hypothyroidism, and liver enzyme elevation, may be initially considered attributable to either study intervention. Therefore, evaluation of attribution is important for determining the study intervention most likely related to the AE, or an alternative etiology, and subsequently proper clinical management. The following aspects should be considered:

1. Timing of AE Onset

   Since lenvatinib is administered daily and continuously due to a relatively short half-life (28 hours) and pembrolizumab is administered 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 withheld.

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 irAE 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 rapidly worsens, action, including interrupting both drugs and initiating treatment with a corticosteroid (with the exception of hypothyroidism and type 1 diabetes mellitus) 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 × ULN for more than 2 weeks

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

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

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

Participants who experience a toxicity that is attributable to lenvatinib should modify, interrupt, or discontinue lenvatinib as per the Dose Modification Guidelines for Lenvatinib-Related Adverse Events, but may continue in the trial receiving pembrolizumab, unless or until unacceptability toxicity or progression occurs. Participants who experience a toxicity attributable to pembrolizumab should interrupt or discontinue pembrolizumab as per Dose Modification Guidelines for Pembrolizumab Related Adverse Events, but may continue in the trial receiving lenvatinib, unless or until unacceptable toxicity or progression occurs.

6.7.5 Other Allowed Dose Interruptions

If a participant receiving lenvatinib requires surgery during the study, the stopping and restarting times for lenvatinib should be as follows:

- For minor procedures, stop lenvatinib at least 2 days before the procedure and restart it at least 2 days afterward, once there is evidence of adequate healing and no risk of bleeding.

- For major procedures, stop lenvatinib at least 1 week (5 half-lives) before the surgery and restart it at least 2 weeks afterward, once there is evidence of adequate healing and no risk of bleeding.

Pembrolizumab may be interrupted for situations other than treatment-related AEs, such as medical/surgical events or logistic reasons not related to study therapy. Participants should be returned to study therapy 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. Imaging should not be delayed for delays in treatment cycles.

6.7.6 Docetaxel

Refer to the approved product label for docetaxel.

6.8 Intervention After the End of the Study

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

6.9 Clinical Supplies Disclosure

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

6.10 Standard Policies

Not applicable.

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.

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.

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

- ALT or AST elevation meeting the following criteria:
  - ALT or AST >5X ULN for more than 2 weeks
    - Pembrolizumab will have already been permanently discontinued per Table 4, but lenvatinib may be administered at a reduced dose by the time this criterion is met and must be permanently discontinued immediately.
  - ALT or AST >3X ULN and (TBL >2X ULN or INR >1.5)
    - Although Table 4 advises pembrolizumab to be withheld (interrupted), and Table 3 advises lenvatinib to have no dose modification or a reduction, if this criterion is met, both drugs must be permanently discontinued immediately.
- The participant or participant's legally acceptable representative (see Appendix 7, Section 10.7.1) requests to discontinue study intervention.
- The participant interrupts study intervention administration for more than 28 days for lenvatinib or >12 weeks for pembrolizumab or docetaxel, except if agreed to by the Sponsor.
- The participant has a medical condition or personal circumstance that, in the opinion of the investigator and/or Sponsor, places the participant at unnecessary risk from continued administration of study intervention.

- The participant has a confirmed positive serum pregnancy test.

- PD is radiographically documented and verified by BICR per RECIST 1.1 and, when clinically appropriate, confirmed by the site per iRECIST.

    - **Note:** If a participant has unconfirmed PD and is clinically stable, the assigned study intervention per protocol may be continued at the investigator's discretion until PD is confirmed at least 28 days from the date of imaging suggesting PD. If subsequent imaging does not confirm PD, the participant should continue to receive study intervention and imaging to monitor disease status, as defined in Section 1.3.

- If a participant has confirmed PD per RECIST 1.1, it is recommended that the participant be discontinued from the study unless, in the investigator's opinion, the participant is deriving benefit from study intervention. Clinically stable** participants may continue to receive study intervention after consultation with the Sponsor.

- **Clinical stability is defined as:

    - Absence of symptoms and signs (including worsening of laboratory values) indicating clinically significant PD.

    - No decline in ECOG performance status.

    - Absence of PD or progressive tumor at critical anatomic sites (eg, cord compression) requiring urgent alternative medical intervention.

- The participant has intercurrent illness preventing further administration of study intervention.

- The participant has any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment. Exceptions to secondary malignancy 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 therapy or follow-up.

- The participant has unacceptable toxicities (Section 6.6).

- Administrative reasons requiring cessation of study intervention.

- The participant has recurrent Grade 2 pneumonitis.

- Local treatment guidelines for docetaxel.

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 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.

The maximum amount of blood collected from each participant over the duration of the study will be provided in the Laboratory Manual. Repeat or unscheduled samples may be collected for safety reasons or because of technical issues with the samples.

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 (see Appendix 7, Section 10.7.1) 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 study protocol number, study

protocol title, dated signature, and agreement of the participant (or his/her 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 ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's 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 the study and the study population are to be included in the study informed consent form.

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, site personnel will add the allocation number to the participant identification card.

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

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that is considered to be clinically significant by the investigator. Details regarding the

participant's lung cancer will be recorded separately and not listed as medical history. The medical history will also include an assessment of smoking history.

The investigator or qualified designee will obtain prior and current details regarding the participant's lung cancer.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

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

Prior anticancer treatment: **The investigator or qualified designee will review and record all prior anticancer treatments including systemic treatments, radiation, and surgeries, regardless of the time before the first dose of study intervention. This will include platinum doublet chemotherapy and anti-PD-1/PD-LI therapy**.

8.1.5.2 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 before the first dose of Second Course study intervention, during Second Course treatment, and for 30 days after the last dose of Second Course study intervention (or 90 days if used to treat an SAE) will be recorded.

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 study intervention 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 of screening/rescreening visit requirements are provided in Section 8.10.1.

8.1.7 Assignment of Allocation 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 randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

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

8.1.8 Study Intervention Administration

Pembrolizumab or docetaxel: Administration of pembrolizumab or docetaxel will be witnessed by the investigator and/or study staff and or qualified designee per institutional guidelines and procedures.

Lenvatinib: Lenvatinib (20 mg [two 10-mg capsules] in Arm 1 and 24 mg [two 10-mg capsules and one 4-mg capsule] in Arm 3) will be administered in the clinic on Day 1 of each cycle. In Arm 1 only, lenvatinib will also be administered in the clinic on Day 15 of Cycle 1 in the initial treatment phase. Lenvatinib will be taken at home (at approximately the same time each day) for all non-clinic doses in the initial treatment phase and in the Second Course phase.

8.1.8.1 Timing of Dose Administration

Pembrolizumab: Pembrolizumab will be administered as a 30-minute IV infusion on Day 1 of each 21-day cycle. Sites should make every effort to target the infusion time 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 to +10 minutes is permitted (ie, infusion time is 30 minutes: –5min /+10 min).

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

Lenvatinib: Lenvatinib 20 mg (Arm 1) and 24 mg (Arm 3) will be taken orally once daily with water (with or without food) in 21-day cycles. On Day 1 of each cycle, participants in Arm 1 will receive lenvatinib 0 to 4 hours after the pembrolizumab infusion.

Participants will take lenvatinib at home on all other non-clinic days. If a lenvatinib dose is missed and cannot be taken within 12 hours, that day's dose should be skipped, and the next dose should be taken at the usual time of administration.

Docetaxel: Docetaxel 75 mg/m^2 will be administered as a 60-minute IV infusion every 3 weeks on Day 1 of each 21-day cycle. Sites should make every effort to target the infusion time to be as close to 60 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 60 minutes: -5 min/+10 min).

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

All participants receiving docetaxel should be premedicated with oral or injectable steroids according to the approved product label and/or standard practice. Additional premedications should be administered as per standard practice.

8.1.8.2 Compliance

Pembrolizumab or docetaxel: Administration of pembrolizumab or docetaxel will be witnessed by the investigator and/or qualified designee. The total volume of study intervention infused will be compared with the total volume prepared to determine compliance with each dose administered.

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

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.

When a participant withdraws from participation in the study, all applicable activities scheduled for the final study 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.

8.1.10 Participant Blinding/Unblinding

This is an open-label study.

8.1.11 Calibration of Equipment

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

8.1.12 Demographics

Participant demographic information will be collected at the screening visit. Demographic information includes date of birth (or age), sex, and race/ethnicity.

8.1.13 Subsequent Antineoplastic Treatment

The investigator or qualified designee will review all new antineoplastic treatment initiated after the last dose of study intervention. Once new antineoplastic treatment has been initiated, the participant will move into survival follow-up. All antineoplastic treatment 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 email.

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

As of Amendment 09, participants will no longer require tumor response assessments by BICR to be performed. Scans will no longer be submitted to the iCRO. Participants 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.

The process for collection and transmission of images to the CIV is provided in the Site Imaging Manual. CT is strongly preferred for tumor imaging. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. MRI is the strongly preferred modality for imaging the brain. The same imaging modality, ideally the same scanner, and contrast administration should be used for a participant throughout the study to optimize reproducibility of the assessment of existing and new tumor burden and improve the accuracy of assessment of response or progression based on imaging.

Note: For the purposes of assessing tumor imaging, the term "investigator" refers to the local investigator at the site and/or the radiologic reviewer 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 images for all study participants from the sites will be submitted to the CIV. In addition, images (including those via other modalities) that are obtained at an unscheduled time point to determine PD, as well as images obtained for other reasons, but, which demonstrate radiologic progression, should be submitted to the CIV.

When the investigator identifies radiographic progression per RECIST 1.1, the CIV will perform expedited verification of radiologic PD and communicate the results to the trial site and Sponsor (see Section 8.2.1.6 and Figure 3). Study intervention should continue until PD has been verified. Regardless of whether PD is verified, if the investigator considers the participant to have progressed but elects to implement iRECIST, the investigator will assess for confirmation of progression by iRECIST at subsequent time points. Images should continue to be submitted to the CIV.

8.2.1.1 Pretrial Imaging to Confirm Disease Progression

The site's study team must have reviewed images from at least 2 dates to confirm that radiographic progression has occurred per RECIST 1.1 on or after an anti-PD-1/PD-L1 treatment. These images will be submitted to the CIV before randomization and should include the following:

- Imaging prior to anti-PD-1/PD-L1 treatment or an image showing nadir during anti-PD-1/PD-L1 treatment.
- Imaging to determine that radiographic progression has occurred per RECIST 1.1 within 12 weeks (84 days) from the last dose of an anti-PD-1/PD-L1mAb.

- **Note:** These scans may be from the baseline screening for the study.

The CIV must have received these images before randomization to confirm that the images are of diagnostic quality.

8.2.1.2 Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 30 days before the date of randomization. The site study team must review screening images to confirm that the participant has measurable disease per RECIST 1.1.

Brain imaging will be performed in all participants at screening within 30 days before the date of randomization. When brain imaging is performed, MRI should be used if possible. If MRI is medically contraindicated, or is medically inappropriate, then CT with contrast is an acceptable alternative.

Imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if it is of diagnostic quality, is performed within 30 days before the date of randomization, and can be assessed by the CIV.

8.2.1.3 Tumor Imaging During the Study

The first on study imaging assessment should be performed at **6 weeks (42 days +7 days)** and again at **12 weeks (84 days +7 days)** from the date of randomization. Subsequent tumor imaging should be performed every 6 weeks (42 days ±7 days), or more frequently if clinically indicated. After 36 weeks, participants who remain on study intervention will have imaging performed every 9 weeks (63 days ±7 days). Following Week 54, participants who remain on study intervention will have imaging performed every 12 weeks (84 days ±7-days). **Note: Imaging timing should follow calendar days and not be adjusted for delays in cycle starts and/or acquisition of unscheduled imaging.** Imaging should continue to be performed until PD is identified by the investigator and verified by the CIV (unless the investigator elects to continue study intervention and follow iRECIST), the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first. All supplemental imaging must be submitted to the CIV if imaging shows PD or to support response assessments.

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

Per iRECIST (Section 8.2.1.7), PD 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 with unconfirmed PD may continue on study intervention at the discretion of the investigator until progression is confirmed by the site, provided they have met the criteria for

clinical stability detailed in Section 8.2.1.7. Participants who have confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point if participants are clinically stable. Participants with confirmed PD per iRECIST, as assessed by the site, will discontinue study intervention. Exceptions are detailed in Section 8.2.1.7.

8.2.1.4 End of Treatment and Follow-up Tumor Imaging

As of Amendment 09, further follow-up tumor imaging is only required for participants who are candidates for Second Course treatment.

For participants who discontinue study intervention, tumor imaging should be performed at the time of study intervention discontinuation (±4-week window). If previous imaging was obtained within 4 weeks before the date of discontinuation, imaging at study intervention discontinuation is not mandatory. For participants who discontinue study intervention because of documented PD, this is the final required tumor imaging if the investigator elects not to implement iRECIST. All images should be submitted to the CIV.

For participants who discontinue study intervention without documented PD, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule as during study intervention (every 6 weeks until Week 36, every 9 weeks until Week 54, and then every 12 weeks or more frequently if clinically indicated), until the start of new anticancer treatment, PD, pregnancy, death, withdrawal of consent, or the end of the study, or notification by the Sponsor, whichever occurs first.

8.2.1.5 Second Course Retreatment Tumor Imaging

Tumor imaging must be performed within 30 days before Second Course Cycle 1 of pembrolizumab. Local investigator assessment with site radiology department reading will be used to determine eligibility for Second Course treatment. All Second Course images should be submitted to the CIV for quality control, storage, and possible retrospective review.

The first on study imaging assessment should be performed 12 weeks (84 ±7 days) after Cycle 1. Subsequent tumor imaging should be performed every 12 weeks (±7 days) or more frequently, if clinically indicated.

Per iRECIST (Section 8.2.1.7), if tumor imaging shows initial PD, tumor assessment should be repeated 4 to 8 weeks later to confirm PD with the option of continuing study intervention while awaiting radiologic confirmation of PD. Participants who have confirmatory imaging do not need to undergo scheduled tumor imaging if it is less than 4 weeks later and may wait until the next scheduled imaging time point if they are clinically stable.

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

For participants who discontinue Second Course treatment, tumor imaging should be performed at the time of study intervention discontinuation (±4 weeks). If previous imaging was obtained within 4 weeks before the date of discontinuation, imaging at study intervention discontinuation is not mandatory. For participants who discontinue study intervention due to documented PD, this is the final required tumor imaging.

For participants who discontinue Second Course treatment without documented PD, every effort should be made to continue monitoring disease status with imaging every 12 weeks (±7 days) until the start of a new anticancer treatment, PD, death, withdrawal of consent, or the end of the study, or notification by the Sponsor, whichever occurs first.

8.2.1.6 RECIST 1.1 Assessment of Disease

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

Figure 3 illustrates the imaging flow involving verification of PD for clinically stable participants.

8.2.1.7 iRECIST Assessment of Disease for Immune-based Therapeutics

iRECIST is based on RECIST 1.1 but is 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 PD is confirmed by the investigator working with the local radiologist, according to the rules outlined in Appendix 8. This allowing of continued treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy and can then experience subsequent disease response. These data will be captured in the clinical database.

Tumor flare includes any of the following scenarios:

- Worsening of existing target lesion(s)
- Worsening of existing nontarget lesion(s)
- Development of new lesions(s)

**Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant PD

- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care.

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

If the investigator decides to continue study intervention, the participant may continue receiving study intervention, and tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment. Images should continue to be sent to the CIV for retrospective BICR.

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

If a participant has confirmed radiographic PD as defined in Appendix 8, study intervention should be discontinued. However, if the participant is achieving 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, imaging should continue at the intervals outlined in Section 1.3, and images should be submitted to the CIV.

A description of the adaptations and iRECIST process is provided in Appendix 8, with additional details in the iRECIST publication [Seymour, L., et al 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 6 and illustrated as a flow chart in Figure 3.

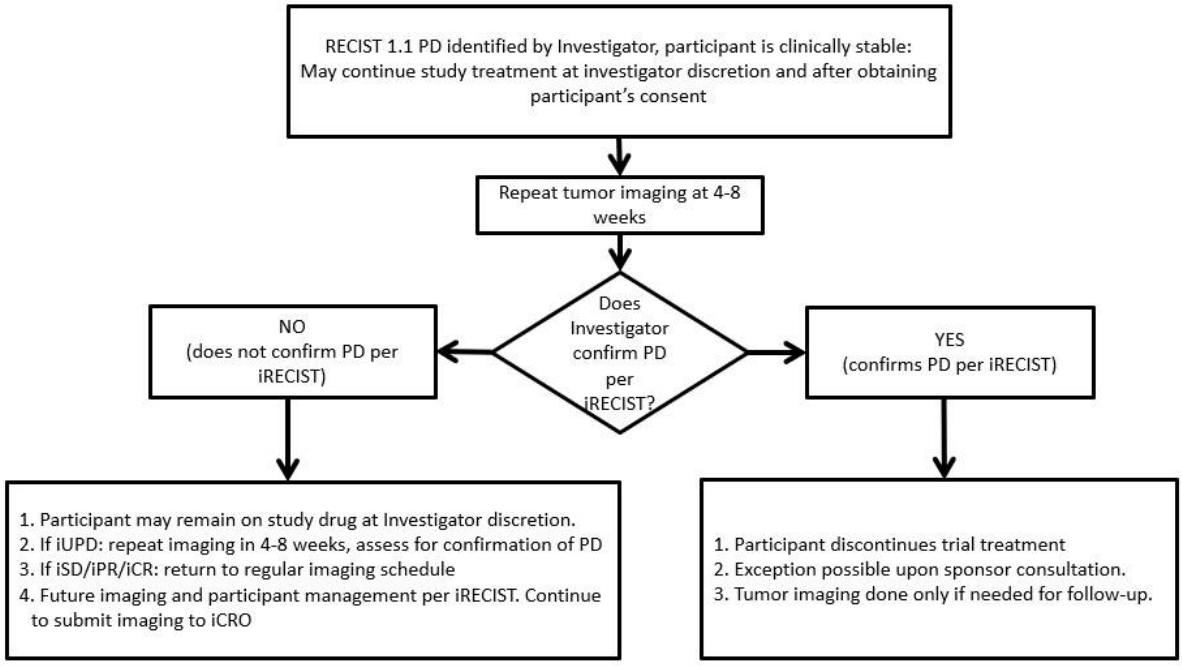
Table 6 Summary of Imaging and Treatment Requirements After First Radiologic Evidence of Disease Progression

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1 per investigator assessment.	Submit the imaging to BICR for verification. Repeat imaging at 4 to 8 weeks to confirm PD per iRECIST.	May continue study intervention at the investigator's discretion and after obtaining participant's consent.	Submit the imaging to BICR for verification.	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.	Continue study intervention at the investigator's discretion.	No additional imaging required.	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.	No additional imaging required.	Discontinue treatment.

Abbreviations: BICR = blinded independent central review; CIV = central imaging vendor; iCPD = iRECIST-confirmed progressive disease; iCR = iRECIST-confirmed complete response; iPR = iRECIST-confirmed partial response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST-confirmed 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 PD has been centrally verified, further management is by the site, based on iRECIST. Any further images should still be submitted to the CIV, but no rapid review will occur. If RECIST 1.1 PD has not been centrally verified, ideally the site should continue study intervention. Whether or not study intervention continues, images should be collected and submitted to the CIV with VOP request until RECIST 1.1 PD is verified by BICR.

Figure 3 Imaging and Treatment for Clinically Stable Participants Treated With Pembrolizumab After First Radiologic Evidence of Progressive Disease Assessed by the Investigator



8.2.1.8 Tumor Tissue Collection

The archival tumor tissue sample is a sample obtained any time from initial diagnosis of NSCLC and prior to receiving immunotherapy (anti-PD-1/PD-L1 mAb) and is to be submitted before randomization for PD-L1 status and stratification.

The newly obtained tissue biopsy is a sample obtained after completion of immunotherapy (anti-PD-1/PD-L1 mAb) from a core or excisional biopsy of a tumor lesion not previously irradiated (fine-needle aspiration is not adequate) submitted to a central laboratory before randomization. No systemic anticancer therapy may be administered between the newly obtained tissue sample and initiation of study treatment.

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

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

Rationale for archival and newly obtained tissue biopsy: Evaluating the differences between archival and newly obtained biopsies at the molecular level may help provide

information on the underlying biology contributing to resistance mechanisms associated with immune-checkpoint inhibitors. It is hypothesized that patients who are refractory to immune-checkpoint inhibitors may harbor certain biological characteristics such as increased angiogenesis and epithelial-mesenchymal transition/stroma signaling. Analysis examining both an archival and a newly obtained tumor sample with prior information on the outcome of treatment with checkpoint inhibitors could help confirm if these possible resistance features exist and may help explain how some patients are more likely to benefit from pembrolizumab (anti-PD-1) + lenvatinib (VEGFR inhibitor) combination therapy.

8.2.2 Patient-reported Outcomes

As of Amendment 09, 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.

Collection of ePRO data is required for all participants, as noted in the SoA (Section 1.3.1 and Section 1.3.2). The EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L questionnaires will be administered by trained site personnel and completed electronically by participants in the following order: 1) EORTC QLQ-C30; 2) EORTC QLQ-LC13; 3) EQ-5D-5L. The questionnaires should be administered before dosing:

- At every cycle through Cycle 17
- At every other cycle through Cycle 35 (eg, Cycles 1-17, 19, 21, 23, 25, 27, 29, 31, 33, and 35)
- At the End of Treatment (EOT) visit
- At the 30-day Safety Follow-up visit

If the EOT visit takes place ≥30 days after the last dose of study intervention and is combined with the Safety Follow-up visit, PRO assessments only need to be performed at that visit.

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

8.3 Safety Assessments

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

8.3.1 Physical Examinations

During the screening period, a complete physical examination including oral examination will be performed by an investigator or medically qualified designee (consistent with local requirements) per the institutional standard as specified in the SoA (Section 1.3). Height and weight will also be measured and recorded. Documentation of the physical examination will be included in the source documentation at the investigational site. Significant findings before participant randomization will be recorded on the appropriate eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the appropriate eCRF.

For cycles that do not require a complete physical examination, a brief directed physical examination including oral examination will be performed by the investigator or medically qualified designee (consistent with local requirements) per the institutional standard as specified in the SoA (Section 1.3). After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital Signs

- Vital sign measurements (ie, systolic and diastolic BP [mm Hg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in the SoA (Section 1.3) by a validated method.
- Blood pressure and pulse will be measured after the participant has been resting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.
- Only 1 BP measurement is needed for participants with systolic BP <140 mm Hg and diastolic BP <90 mm Hg. If the participant's initial BP 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, investigators and 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. 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 as designated in the SoA (Sections 1.3.1 and 1.3.2). MUGA or ECHO scans should be performed locally in accordance with the institution's standard practice. MUGA scans are the preferred modality. However, whichever modality is used for an individual participant at baseline should be repeated for all subsequent LVEF assessments for that participant. LVEFs as assessed by the institution will be entered on the eCRF. Investigator assessment will be based on institutional reports.

8.3.5 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).
- For any laboratory tests with values considered clinically significantly abnormal during participation In the study or within 30 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.5.1 Laboratory Safety Evaluations (Hematology, Chemistry, and Urinalysis)

8.3.5.1.1 Hematology and Clinical Chemistry

Hematology and clinical chemistry assessments will be performed within 10 days before administration of the first dose of study intervention, and within 3 days of dosing for all subsequent scheduled visits. The results must be reviewed before administration of study therapy. Electrolytes such as potassium, calcium, and magnesium should be monitored and abnormalities, when considered clinically significant, should be corrected in all participants before starting study intervention.

8.3.5.1.2 Urine Dipstick Testing/Urinalysis

Urine dipstick testing or urinalysis will be performed locally within 10 days before the start of study intervention. Urine dipstick testing will only be performed in participants taking lenvatinib. After screening, urine dipstick testing will be performed at every cycle while participants are taking lenvatinib and urinalysis will be performed at Cycle 6 and every 6 cycles thereafter (Cycles 12, 18, 24, etc.). At visits when urinalysis is obtained the urine dipstick is not required. The sample can be collected within 3 days of Day 1 of each cycle (Section 1.3.1 and Section 1.3.2). During Second Course treatment, urine dipstick testing will be performed at every cycle only for participants taking lenvatinib, and urinalysis will be performed at Cycle 1 and then at Cycles 6 and 12 (Section 1.3.3).

Once participants are allocated, urine dipstick testing for participants with ≥2+ proteinuria should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles. Urine dipstick testing should be performed at the investigational site. If a new event of ≥2+ proteinuria occurs, Day 15 urine dipstick testing for evaluation of proteinuria must be resumed until results are 1+ (30 mg/dL) or negative for 2 consecutive treatment cycles.

8.3.5.1.3 Thyroid Function Testing

Thyroid function testing will include determination of TSH, T3, and FT4. FT3 determination is acceptable at sites where T3 cannot be assessed. These tests can be performed by the central laboratory if they are unavailable at the local laboratory.

The screening blood sample for thyroid function testing should be obtained within 10 days before the first dose of study intervention.

Thyroid function testing will be performed within 3 days before Day 1 for all participants and at every other cycle beginning with Cycle 2 for participants receiving pembrolizumab and/or lenvatinib. Participants may be dosed in subsequent cycles after Cycle 1 Day 1 while thyroid function test results are pending. However, the results should be reviewed by the investigator when available.

8.3.5.2 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 for urine or within 72 hours for serum before 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 regulations (see Appendix 7).

8.3.6 Eastern Cooperative Oncology Group Performance Status

The investigator or qualified designee will assess ECOG performance status (See Appendix 9) at screening and at each treatment cycle, as specified in the SoA (Section 1.3).

8.4 Adverse Events, Serious Adverse Events, 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.

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity, and causality.

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

All AEs, SAEs, and other reportable safety events that occur after the 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 after 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 after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention allocation/randomization through 120 days following cessation of study intervention, or 30 days following cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside the time specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

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 the investigator 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 7.

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 7 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	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

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

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended, nonleading verbal questioning of the participant is the preferred method of inquiring 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, 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 allocated 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 Reaction (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 SAEs) 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) including the pregnancy of a male participant's female partner, that occurs during the study are reportable to the Sponsor. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Pembrolizumab

It is not known whether pembrolizumab is excreted in human milk. No studies have been conducted to assess the impact of pembrolizumab on milk production or its presence in breast milk. Because many drugs are excreted in human milk, female participants must discontinue breastfeeding during treatment with pembrolizumab and for 4 months after the final dose [U.S. Prescribing Information 2018].

Lenvatinib

It is not known whether lenvatinib is excreted in human milk. However, lenvatinib and its metabolites are excreted in rat milk at concentrations higher than in maternal plasma. Because of the potential for SAEs from lenvatinib in nursing infants, female participants are advised to discontinue breastfeeding during treatment with lenvatinib [U.S. Prescribing Information 2018a].

Docetaxel

It is not known whether docetaxel is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for SAEs from docetaxel in nursing infants a decision should be made whether to discontinue nursing or to discontinue the drug, considering the importance of the drug to the mother [U.S. Prescribing Information 2018b].

See Table 7 for additional details regarding pregnancy.

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

Efficacy endpoints as outlined in this section will not be reported to the Sponsor.

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

The Sponsor will monitor 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 serious and nonserious AEs 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. Lenvatinib overdose without an associated AE is not considered an ECI.

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: ≥5 times the protocol-specified dose
- Lenvatinib: any dose above the protocol-prescribed dose if associated with an AE

There is no specific antidote for an overdose of lenvatinib. Due to its high degree of plasma protein binding, lenvatinib is not expected to be dialyzable. Adverse reactions in patients receiving single doses of lenvatinib as high as 40 mg were similar to those in clinical studies at the recommended dose for differentiated thyroid cancer and RCC. No specific information is available on the treatment of overdose of pembrolizumab or lenvatinib. There is no known antidote for docetaxel overdose. In the event of overdose, the specific intervention should be withheld, and the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Pembrolizumab:

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

Lenvatinib:

- An overdose associated with lenvatinib should be reported as a nonserious event of clinical interest, unless the AE itself meets criteria for an SAE.

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

8.6 Pharmacokinetics

As of Amendment 09, 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.

Blood samples will be collected from the first 90 participants receiving study intervention in Arm 1 (pembrolizumab + lenvatinib) as specified in the SoA (Section 1.3.1). Study sites must have appropriately trained staff and adequate equipment for procuring and processing specimens. Instructions for collection, handling, and shipping of PK samples will be provided in the Laboratory Manual.

If, at some point during enrollment, prospective PK blood sample collection is no longer required, the sites will be notified accordingly.

8.6.1 Blood Collection for Serum Pembrolizumab

To evaluate pembrolizumab immunogenicity and exposure during treatment with pembrolizumab + lenvatinib, sample collections for analysis of antidrug antibodies (ADA) and PK are currently planned for the first 90 participants in Arm 1 (pembrolizumab + lenvatinib), as shown in the SoA (Section 1.3.1). Blood samples will be obtained to measure PK and ADA for serum pembrolizumab. These samples may be stored, and analysis may be performed if required. If ongoing ADA and/or PK results are deemed unnecessary by the Sponsor, it may be decided to discontinue or reduce further sample collection in this study. Should this occur, it will be communicated by an administrative memo. If PK and/or ADA analyses are performed, the results of these analyses will be reported separately.

8.6.2 Blood Collection for Plasma Lenvatinib

Plasma concentrations of lenvatinib coadministered with pembrolizumab (Arm 1) will be measured for the first 90 participants randomized to this treatment arm. Lenvatinib data will be analyzed using a PopPK approach. Lenvatinib will be quantified by validated tandem high-performance liquid chromatography/mass spectroscopy.

8.7 Pharmacodynamics

Not applicable.

8.8 Biomarkers

As of Amendment 09, 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 circulating tumor nucleic acid
- Blood for plasma biomarker analyses
- Blood for serum biomarker analyses
- Archival tumor tissue
- Newly obtained biopsy

Sample collection, storage, and shipment instructions for exploratory biomarker specimens will be provided in the Laboratory Manual.

8.8.1 Planned Genetic Analysis Sample Collection

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

8.9 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data associated with medical encounters will be collected in the eCRF by the investigator and study-site personnel for all participants throughout the study.

Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses. All-cause hospitalizations and emergency room visits must be reported on the eCRF from the time of 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.

8.10 Visit Requirements

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8.

Unscheduled visits are permitted at any time during the study.

8.10.1 Screening

Forty-two days before randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as provided in Section 5. **Note**: Screening procedures may be repeated after consultation with the Sponsor.

Documented informed consent must be obtained before performing any protocol-specific procedures. Results of a test performed before the participant's documented informed consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 42 days before the first dose of study intervention except for the following:

- Laboratory tests are to be performed within 10 days before the first dose of study intervention. An exception is hepatitis and HIV testing, which may be done up to 28 days before the first dose of study intervention, if applicable. Repeated laboratory evaluation to establish eligibility is not allowed unless discussed and agreed upon with the Sponsor.

- Baseline imaging is to be performed within 30 days before the first dose of study intervention.

- ECOG performance status is to be evaluated within 7 days before the date of the first dose of study intervention. If screening ECOG performance status is obtained within 3 days before C1D1, it is not necessary to repeat at C1.

- Full physical examination including an oral examination is to be performed before start of study intervention.

- For WOCBP, a urine pregnancy test will be performed within 24 hours or serum pregnancy test will be performed within 72 hours before the first dose of study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local trial site laboratory).

- If a newly obtained biopsy, meeting all the eligibility requirements, was obtained prior to screening, this sample may be used for the study.

8.10.1.1 Rescreening

Participants may be rescreened after initially failing to meet inclusion/exclusion criteria. Results of assessments during the original screening period are acceptable in lieu of repeat screening tests if obtained within the specified time frame and the corresponding criteria are met. Rescreened participants will retain their original screening numbers.

8.10.2 Initial Treatment

Visit requirements are outlined in the SoA (Section 1.3). Assessments/procedures are to be performed before administration of study intervention.

8.10.2.1 Telephone Contact or Visit

A telephone contact or visit will be conducted on Cycle 1 Day 8 to assess participants for development of early toxicity, as outlined in the SoA (Section 1.3.1).

8.10.3 Second Course Treatment

Note: In alignment with the study-specific investigator letter dated 22-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 or docetaxel can continue treatment per investigator's discretion. Participants who are potential candidates for Second Course treatment will continue in Efficacy Follow-up.

All participants enrolled in the lenvatinib + pembrolizumab arm (Arm 1) who have SD, PR, or CR may be eligible for up to an additional 17 cycles of pembrolizumab treatment if there is radiographic disease progression by investigator assessment after initial treatment or First Course has been completed or stopped for confirmed CR. This retreatment is the Second Course of this study.

Participants in the lenvatinib + pembrolizumab arm (Arm 1) may enter the Second Course if all of the following criteria are also met:

1. The participant received pembrolizumab

2. No new anticancer treatment was administered after the last dose of study intervention

3. The participant meets all of the inclusion criteria and none of the exclusion criteria

4. The study is ongoing

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

Pembrolizumab will be administered every 21 days for up to 17 treatment cycles (approximately 1 year). Treatment may continue until a discontinuation criterion is met (Section 7.1).

The decision of whether to continue lenvatinib during Second Course treatment will be at the discretion of the investigator, provided that lenvatinib was not discontinued due to toxicity. If lenvatinib is continued or restarted, participants will be retreated at the same dose level as when they last received pembrolizumab + lenvatinib. Treatment with lenvatinib will continue until a discontinuation criterion (Section 7.1) is met.

Second Course visit requirements are outlined in the SoA (Section 1.3.3). Specific procedure-related details are provided in Section 8.1.

An objective response or PD occurring during the Second Course phase will not be counted as an event for the primary analysis of either endpoint in this study.

8.10.4 Discontinued Participants Continuing to be Monitored in the Study

The discontinuation visit should take place at the time study intervention is discontinued for any reason. If the discontinuation visit takes place 30 days from the last dose of study intervention, at the time of the mandatory Safety Follow-up visit, the visit is not required. All procedures required at the discontinuation visit and at the 30-day Safety Follow-up visit should be performed.

8.10.5 Posttreatment Visit

8.10.5.1 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 initiation of a new anticancer treatment, whichever comes first.

Participants who are eligible for Second Course retreatment may have up to 2 Safety Follow-up visits, 1 after initial treatment and 1 after Second Course treatment.

8.10.5.2 Follow-up Visits

Participants who discontinue study intervention for a reason other than PD will move into the Follow-up Phase 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, end of study, or the participant begins retreatment as detailed in Section 8.10.3. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated.

Participants who are eligible for retreatment according to the criteria in Section 8.10.3 may move from follow-up to the Second Course Phase if they experience PD. Details are provided in the SoA (Section 1.3.3).

8.10.5.3 Survival Follow-up Contacts

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

8.10.6 Survival Status

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

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If changes are made to primary and/or key secondary hypotheses or the statistical methods related to these hypotheses after the study has begun, but before any unblinding/final database lock, the protocol will be amended (consistent with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] Guideline E9). Changes to the exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but before 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) will be developed to detail PK and biomarker analyses.

9.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Phase 3, randomized, active-controlled, parallel-group, multi-site, open-label study of pembrolizumab + lenvatinib versus docetaxel or lenvatinib in participants with metastatic NSCLC who have PD during/after platinum doublet chemotherapy, and previous exposure to one anti-PD-1/PD-L1 mAb.
Treatment Assignment	Approximately 405 participants will be randomized in a 4:4:1 ratio among 3 treatment arms: pembrolizumab + lenvatinib (Arm 1), docetaxel (Arm 2), and lenvatinib monotherapy (Arm 3). Stratification factors are as follows: • Anti-PD-1/PD-L1 mAb (immediate prior therapy versus not the immediate prior therapy) • PD-L1 TPS (<50% versus ≥50%) • ECOG performance status (0 versus 1)
Analysis Populations	Efficacy: Intention-to-Treat (ITT) Safety: All Participants as Treated (APaT) PRO: Full Analysis Set (FAS) population
Primary Endpoints	• Overall survival (OS) • Progression-free survival (PFS) based on RECIST 1.1 as assessed by BICR
Secondary Endpoints	• Objective response based on RECIST 1.1 as assessed by BICR • DOR based on RECIST 1.1 as assessed by BICR • AEs and discontinuations due to AEs • Scores for global health status/QoL, cough, chest pain, dyspnea, and physical functioning • TTD in global health status/QoL, cough, chest pain, dyspnea, and physical functioning

Statistical Methods for Key Efficacy Analyses	The primary hypotheses will be evaluated by comparing the pembrolizumab + lenvatinib arm to the docetaxel arm using a stratified log-rank test for PFS and OS. 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. The difference in objective response rate (ORR) in pembrolizumab + lenvatinib versus docetaxel will be estimated using the stratified Miettinen and Nurminen method with strata weighting by sample size. The difference in ORR in pembrolizumab + lenvatinib versus lenvatinib will be estimated using the Miettinen and Nurminen method without stratification.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. There is no Tier 1 safety endpoint for this study. Tier 2 parameters will be assessed via point estimates by treatment arm with 95% confidence intervals (CIs) provided for between-arm comparisons of pembrolizumab + lenvatinib to docetaxel; only point estimates by treatment arm are provided for Tier 3 safety parameters. The 95% CIs for the between-treatment differences in percentages will be provided using the Miettinen and Nurminen method.

Interim Analyses	The study includes 1 single-arm futility analysis, 2 interim analyses, and a final analysis:
	- Single-arm futility analysis: 18 participants in the pembrolizumab + lenvatinib arm have been followed up for at least 20 weeks (~10 months after the first participant randomized):
	  - The non-binding criteria for passing futility is to have 1) ≥3 objective responses (ie, confirmed CR or PR) or 2) DCR12 >50% and ≥1 objective response.
	- Interim analysis 1 (IA1): 200 participants in Arms 1 and 2 have been followed up for 6 months (~18 months after the first participant randomized).
	  - Primary purpose: ORR analysis to compare pembrolizumab + lenvatinib to docetaxel
	- Interim analysis 2 (IA2): ~279 PFS events in Arms 1 and 2 have been observed AND at least 6 months follow-up after the last participant is randomized (~36 months after the first participant randomized. ~240 deaths are expected in Arms 1 and 2)
	  - Primary purpose: PFS analysis
	  - Interim OS analysis
	  - ORR analysis to compare pembrolizumab + lenvatinib to lenvatinib monotherapy
	- Final analysis (FA): ~299 deaths have occurred in Arms 1 and 2 AND a minimum of 12 months follow-up after the last participant randomized (~48 months after the first participant randomized)
	  - Primary purpose: Final OS analysis

Multiplicity	The study will use the graphic method of Maurer and Bretz to control multiplicity for multiple hypotheses as well as IAs. The overall Type I error rate over the multiple endpoints will be controlled at 2.5% (1-sided). A small alpha penalty of 0.01% will be paid for single-arm futility analysis. A 0.3% (1-sided) Type I error rate will be initially allocated to test ORR in pembrolizumab + lenvatinib versus docetaxel; 0.29% (1-sided) allocated to test PFS; 1.9% (1-sided) allocated to test OS; and 0% (1-sided) allocated to test ORR in pembrolizumab + lenvatinib versus lenvatinib. Type I errors will be reallocated among the hypotheses of PFS, OS, ORR in pembrolizumab + lenvatinib versus docetaxel, and ORR in pembrolizumab + lenvatinib versus lenvatinib. Lan-DeMets O'Brien-Fleming group sequential methods will be used to allocate α among the interim and final analyses for the OS endpoints.

Sample Size and Power	The planned sample size is approximately 405 participants with 360 participants in either pembrolizumab + lenvatinib or docetaxel arms, and 45 participants in lenvatinib arm. For PFS, based on ~279 events in 360 participants in pembrolizumab + lenvatinib and docetaxel arms and at least 6 months follow-up after the last participant randomized, the study has 93.6% power to detect a HR of 0.60 (pembrolizumab + lenvatinib versus docetaxel) at $\alpha = 0.29\%$ (1-sided), with assumed PFS median of 4.1 months in docetaxel arm. For OS, based on a target number of ~299 events in 360 participants in pembrolizumab + lenvatinib and docetaxel arms, the study has 93.3% power to detect an HR of 0.66 (pembrolizumab + lenvatinib versus docetaxel) at $\alpha = 1.9\%$ (1-sided), with assumed OS median of 8.6 months for the docetaxel arm. For ORR based on the 200 randomized participants in pembrolizumab + lenvatinib and docetaxel arms that were treated for at least 6 months, the study has 80.6% power to detect a 20 percent point increase for pembrolizumab + lenvatinib versus docetaxel at $\alpha = 0.3\%$ (1-sided) (assuming 10% response rate in the docetaxel arm).

9.2 Responsibility for Analyses/In-house Blinding

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

The Sponsor will generate the randomized allocation schedule for study intervention assignment as appropriate in this protocol, and the allocation will be implemented in IRT.

Although the trial is an open-label study, with analyses or summaries generated by study intervention assignment, access to the information of actual treatment received will be limited and documented. Further documentation will be provided in the sSAP. In addition, independent radiologists will perform the central imaging review without knowledge of treatment assignments.

An internal unblinded statistician will monitor the total number of PFS and OS events in the combined pembrolizumab + lenvatinib and docetaxel arms to estimate the timing of the interim analysis. In-house blinding procedures related to the planned interim analyses are described in Section 9.7.

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below.

9.4.1 Efficacy Endpoints

Primary Endpoints

- **OS:** time from randomization to the date of death due to any cause.

- **PFS:** time from randomization to the first documented PD per RECIST 1.1 based on BICR or death due to any cause, whichever occurs first. See Section 9.6.1 for the definition of censoring.

Secondary Endpoints

- **Objective Response:** a confirmed CR or PR per RECIST 1.1 based on BICR. ORR is the proportion of participants with objective response.

- **DOR:** time from the first documented evidence of CR or PR until PD per RECIST 1.1 as assessed by BICR or death due to any cause, whichever occurs first, in participants demonstrating CR or PR.

Tertiary/Exploratory Endpoint

- Disease control at 12 weeks: a CR, PR or SD at 12 weeks per RECIST 1.1 based on BICR. DCR12 is the proportion of participants with disease control at 12 weeks.

9.4.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters, including AEs, SAEs, fatal AEs, laboratory tests, and vital signs. Furthermore, specific events will be collected and designated as ECIs as described in Section 8.4.7.

9.4.3 PRO Endpoints

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

- 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).

- Composite symptom endpoint: cough (QLQ-LC13 Item 31), chest pain (QLQ-LC13 Item 40), or dyspnea (QLQ-C30 Item 8).

- Physical functioning scale (QLQ-C30 Items 1-5).

- TTD for the PRO score 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 1-5) which is defined as the time from baseline to the first onset of a ≥10-point decrease from baseline in PRO score with confirmation by the subsequent visit of a ≥10-point deterioration from baseline in any of the items.

The EQ-5D-5L will be evaluated as an exploratory endpoint.

The analyses and the approach to handling missing data for PRO endpoints will be described in the sSAP.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Population

The analyses of primary efficacy endpoints are based on the intention-to-treat (ITT) population. All randomized participants will be included in this population. Participants will be analyzed in the treatment arm to which they are randomized. Details of the approach to handling missing data are provided in Section 9.6.1.5.

9.5.2 Safety Analysis Population

The APaT population will be used for the analysis of safety data. The ApaT population consists of all allocated participants who receive at least 1 dose of study intervention. Participants will be analyzed in the treatment arm corresponding to the study intervention they actually receive. For most participants, this will be the treatment arm to which they are assigned. Participants who receive 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 intervention for all other cycles, will be analyzed according to the correct treatment arm, and a narrative will be provided for any events that occur during the cycle for which the participant is incorrectly dosed.

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

9.5.3 Pharmacokinetic Analysis Population

The population for PK analysis includes the first 90 participants in the pembrolizumab + lenvatinib arm (Arm 1) who have received at least 1 dose of study intervention with documented dosing history and have measurable plasma levels of lenvatinib or serum levels of pembrolizumab.

9.5.4 PRO Analysis Population

The PRO analyses are based on the PRO full analysis set (FAS) population, defined as randomized participants who have at least 1 PRO assessment available and have received at least 1 dose of study intervention. PRO data will be collected in all participants.

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

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

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

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.

9.6.1.1 Overall Survival

The nonparametric Kaplan-Meier method will be used to estimate the survival curves in each treatment arm. Formal hypothesis testing will be conducted to compare pembrolizumab + lenvatinib versus docetaxel. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR). The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for allocation (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 Restricted Mean Survival Time method may be conducted for OS to account for the possible nonproportional hazards effect and to estimate the absolute benefit of experimental treatment.

9.6.1.2 Progression-free Survival

The nonparametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment arm. Formal hypothesis testing will be conducted to compare pembrolizumab + lenvatinib versus docetaxel. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for allocation (Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model. Analysis using the Restricted Mean Survival Time method may be conducted for PFS to account for the possible nonproportional hazards effect and to estimate the absolute benefit of experimental treatment.

Since PD is assessed periodically, PD can occur any time in the interval between the last assessment when PD is not documented and the assessment when PD is documented. For the primary analysis, for participants with PD, the true date of PD will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1, based on BICR by the CIV. Death is always considered as a confirmed PD event. Participants who do not experience a PFS event will be censored at the last disease assessment. Sensitivity analyses will be performed for comparison of PFS based on the investigator's assessment.

To evaluate the robustness of the PFS endpoint per RECIST 1.1 based on BICR by the CIV, 1 primary and 2 sensitivity analyses with a different set of censoring rules will be performed.

For the primary analysis, if the events (PD or death) are immediately after more than 1 missed disease assessment, the data are censored at the last disease assessment before the missed visits. Data after new anticancer therapy are censored at the last disease assessment before the initiation of new anticancer therapy. The first sensitivity analysis follows the ITT principle (ie, PD/deaths are counted as events regardless of missed study visits or initiation of new anticancer therapy). The second sensitivity analysis considers discontinuation of treatment due to reasons other than CR or initiation of new anticancer treatment, whichever occurs later, to be a PD event for participants without documented PD or death. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for primary and sensitivity analyses are summarized in Table 8.

Table 8 Censoring Rules for Primary and Sensitivity Analyses of Progression-free Survival

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
PD or death documented after ≤1 missed disease assessment, and before new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Censored at last disease assessment before 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
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if participant is still receiving study treatment or has completed study treatment
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment
Abbreviation: PD = progressive disease			

9.6.1.3 Objective Response

Formal hypothesis testing of ORR in pembrolizumab + lenvatinib versus docetaxel at IA1 will be conducted, as secondary efficacy analysis, to support the efficacy of pembrolizumab + lenvatinib over docetaxel, in addition to OS and PFS analysis. Formal hypothesis testing of ORR in pembrolizumab + lenvatinib versus lenvatinib at IA2, as a secondary efficacy

analysis, will be conducted to evaluate the efficacy of pembrolizumab + lenvatinib over lenvatinib.

The Miettinen and Nurminen method will be used for the pairwise comparison of the ORR. The difference in ORR in pembrolizumab + lenvatinib versus docetaxel 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 allocation (Section 6.3.2) will be used as stratification factors in the analysis. The Miettinen and Nurminen method without stratification will be used for comparison of ORR in pembrolizumab + lenvatinib versus lenvatinib and ORR in lenvatinib versus docetaxel.

9.6.1.4 Duration of Response

For participants with a CR or PR, DOR is defined as the time from first documented evidence of CR or PR until PD or death due to any cause, whichever occurs first. Censoring rules for DOR are summarized in Table 9. DOR will be assessed using RECIST 1.1 by BICR.

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

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

Table 9 Censoring Rules for Duration of Response

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anticancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anticancer therapy initiated	Last adequate disease assessment before new anticancer therapy was initiated	Censor (non-event)
Death or progression immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Earlier date of last adequate disease assessment before ≥2 missed adequate disease assessments and new anticancer therapy, if any	Censor (non-event)
Death or progression after ≤1 missed disease assessments and before new anticancer therapy, if any	PD or death	End of response (Event)
A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.		

9.6.1.5 Analysis Strategy for Key Efficacy Endpoints

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 10.

Table 10 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses (Pembrolizumab + Lenvatinib versus Docetaxel)			
OS	Testing: stratified log-rank test Estimation: stratified Cox model with Efron's tie-handling method	ITT	Censored at last known alive date
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 8
Secondary Analyses (Pembrolizumab + Lenvatinib versus Docetaxel)			
Objective Response (RECIST 1.1) by BICR	Testing and estimation: Stratified Miettinen and Nurminen method with stratification	ITT	Participants with missing data are considered nonresponders
DOR (RECIST 1.1) by BICR	Summary statistics using Kaplan-Meier method	All responders in ITT	Censored according to rules in Table 9
Secondary Analyses (Pembrolizumab + Lenvatinib versus Lenvatinib)			
Objective Response (RECIST 1.1) by BICR	Testing and estimation: Miettinen and Nurminen method without stratification	ITT	Participants with missing data are considered nonresponders
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

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

The analysis of safety results will follow a tiered approach (Table 11). The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as system organ class terms) and events that meet predefined limits of change 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 adverse events of special interest (AEOSIs) 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 by treatment arm. In addition, 95% CIs for differences in the proportion of participants with events between pembrolizumab + lenvatinib and docetaxel will be provided 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 either the pembrolizumab + lenvatinib or docetaxel 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 either the pembrolizumab + lenvatinib or docetaxel treatment arm) and SAEs (≥5% of participants in either the pembrolizumab + lenvatinib or docetaxel arm) 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 laboratory, vital signs, and ECG parameters, summary statistics for baseline, on-treatment, and change from baseline values may be provided by treatment arm in table format.

Table 11 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE (≥10% of participants in either the pembrolizumab + lenvatinib or docetaxel arm)	X	X
	Any Grades 3 to 5 AE (≥5% of participants in either the pembrolizumab + lenvatinib or docetaxel arm)	X	X
	Any serious AE (≥5% of participants in either the pembrolizumab + lenvatinib or docetaxel arm)	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. 95% CI for treatment comparison between pembrolizumab + lenvatinib and docetaxel will be performed.			

The safety data in the lenvatinib monotherapy arm (Arm 3) will be summarized by descriptive statistics separately.

9.6.3 Statistical Methods for Patient-Reported Outcomes

Change from baseline in the following secondary PRO endpoints from the EORTC QLQ C30 and EORTC QLQ-LC13 will be assessed:

- Global health status/QoL score (EORTC QLQ-C30 Items 29 and 30)
- Cough score (EORTC QLQ-LC13 Item 31)
- Chest pain score (EORTC QLQ-LC13 Item 40)
- Dyspnea score (EORTC QLQ-C30 Item 8)
- Physical functioning score (QLQ-C30 Items 1 to 5)

A constrained longitudinal data analysis model will be applied, with the PRO score as the response variable, and treatment, time, treatment by time interaction, and clinical trial stratification factors as covariates. Least squares mean change from baseline will be summarized for each outcome. Treatment effect on PRO score change from baseline will primarily be evaluated at Week 12. If the overall PRO completion or compliance rates at Week 12 are less than 60% or 80%, respectively, then the analysis time point will be moved to the next earliest time point in which the rates are at least 60% for completion and at least 80% for compliance. The difference in the least squares mean change from baseline will be reported at the primary analysis time point.

Descriptive analyses will assess the empirical mean change (with 95% CI)from baseline across all time points. Details of PRO analyses will be described in the sSAP.

The Kaplan-Meier method will be used to estimate the TTD survival curves for 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 to 5) in each treatment arm. In addition, TTD survival curves will be estimated for the composite endpoint of cough, chest pain, or dyspnea by treatment arm. Stratified Cox proportional hazards models with Efron's method of tie handling will be used to assess the magnitude of the treatment difference for pembrolizumab + lenvatinib compared with docetaxel. Stratification factors used for allocation will be used in the stratified Cox proportional hazards models. The HR, 95% CI, and nominal *p* value will be reported.

Details of additional PRO analyses will be included in the sSAP.

9.6.4 Summaries of Baseline Characteristics

The comparability of the treatment arms for each relevant demographic and baseline characteristic will be assessed using tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants randomized and the primary reason for discontinuation will be displayed. Demographic variables (such as age) and baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables. The reasons for exclusion from the ITT population (if any) will be summarized.

9.7 Interim Analyses

The treatment-level results of the interim analyses will not be shared with the investigator before completion of the study.

An eDMC will review the unblinded efficacy results and accumulating safety data at planned interim analyses. Treatment-level results of the interim analyses will be provided by the internal unblinded statistician to the eDMC. The eDMC responsibilities and review schedules will be outlined in the Data Monitoring Committee (DMC) Charter. The recommendations of the eDMC will be communicated to the Executive Oversight Committee (EOC). If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, the EOC, and possibly other limited numbers of additional Sponsor personnel, may be unblinded to results at the treatment level to act on these recommendations. Participant-level unblinding to support regulatory filing, should this occur before the end of the study, will be restricted to a designated Sponsor team, who will have no other responsibilities associated with the study. The extent to which individuals are unblinded with respect to the results will be documented. Additional logistical details, revisions to the above plan, and data monitoring guidance will be provided in the eDMC charter.

9.7.1 Safety Interim Analyses

The eDMC will review accumulating safety data periodically to provide an opportunity to terminate the study early if there are safety concerns. The timing of the safety monitoring will be specified in the eDMC charter.

9.7.2 Efficacy Interim Analyses

Futility Analysis

A single-arm futility check will occur when 18 participants treated in the pembrolizumab + lenvatinib arm have at least 20 weeks of follow-up. The futility analysis is intended to evaluate objective response and disease control at 12 weeks in the first 18 participants treated with pembrolizumab + lenvatinib with at least 20 weeks of follow-up. The analysis will likely occur approximately 10 months after study initiation.

In addition, the objective response and disease control at 12 weeks for participants treated with pembrolizumab + lenvatinib who have at least 12 weeks of follow-up at the time of the futility analysis will be evaluated as supportive analyses for the futility assessment. It is estimated that, by the time of the single-arm futility analysis, approximately 100 participants will have been randomized into the study. It is estimated that 35 participants (of approximately 45 randomized into the pembrolizumab + lenvatinib arm) will be eligible for these supportive analyses.

For the evaluation of objective response, participants will be coded as responders if they have an objective response (ie, confirmed CR or PR). Participants not known to have an objective response will be considered as nonresponders.

For evaluation of DCR12, participants will be considered to have disease control at 12 weeks if they have CR, PR, or SD at 12 weeks (±2-week window). Participants will also be considered to have disease control at 12 weeks if they have CR, PR or SD in the first imaging assessment, and have nonevaluable or no imaging assessment at 12 weeks (±2-week window), and subsequent assessment shows CR, PR, or SD before the timing of futility check. Participants not known to have disease control at 12 weeks before the timing of futility check will be considered as not having disease control at 12 weeks.

The non-binding criteria for passing futility are: 1) there are 3 or more objective responses among the first 18 participants treated with pembrolizumab + lenvatinib or 2) DCR12 is >50% and there is at least 1 objective response among the first 18 participants treated with pembrolizumab + lenvatinib. If neither of these criteria is met, the continuation of the study will be reassessed by the EOC considering the totality of the data for pembrolizumab + lenvatinib. The probability of passing the futility analysis based on ORR and DCR12 is shown in Table 12.

Table 12 Probability of Passing Single-arm Futility Analysis

ORR	Difference Between DCR12 and ORR					
	+0.25	**+0.3**	**+0.35**	**+0.4**	**+0.45**	**+0.5**
0.05	8.6	12.2	18.1	25.9	34.7	43.3
0.1	34.1	40.6	49.1	58.6	67.6	75.0
0.15	62.7	69.0	75.8	82.3	87.6	91.2
0.2	83.1	87.2	91.1	94.1	96.2	97.4
0.25	93.9	95.8	97.4	98.5	99.1	99.3

Abbreviations: DCR12 = disease control rate at 12 weeks; ORR = objective response rate.

For example, if the true ORR is 25% and the difference between DCR12 and true ORR is 30% (ie, the DCR12 is 55% [25% + 30%]), the probability of passing the futility analysis based on these criteria is 95.8%.

Efficacy Analyses

In addition, 2 interim analyses (IAs) are planned in addition to the final analyses. The analyses, endpoints evaluated, and drivers of timing are summarized in Table 13.

Table 13 Summary of Efficacy Analysis in Interim and Final Analyses

Analyses	Key Endpoints	Timing*	Estimated Time After First Participant Randomized	Primary Purpose of Analysis
IA1	Objective response	200 participants* have been followed up for 6 months.	~18 months	ORR analysis (pembrolizumab + lenvatinib versus docetaxel)
IA2	PFS OS Objective response	~279 PFS events* have been observed and a minimum of 6 months follow-up after last participant randomized. ~240 death events are expected.	~36 months	Final PFS analysis Interim OS analysis ORR analysis (pembrolizumab + lenvatinib versus lenvatinib)
Final Analysis	OS	~299 death events* have been observed and a minimum of 12 months follow-up after last participant randomized.	~48 months	Final OS analysis

*Timings of IA1 and final analysis are based on the number of participants or events in Arm 1 and Arm 2. Timing of IA2 is based on number of events in Arm 1 and Arm 2 AND at least 6 months after the last participant is randomized.

Timing of final analysis is based on number of events in Arm 1 and Arm 2 AND at least 12 months after the last participant is randomized.

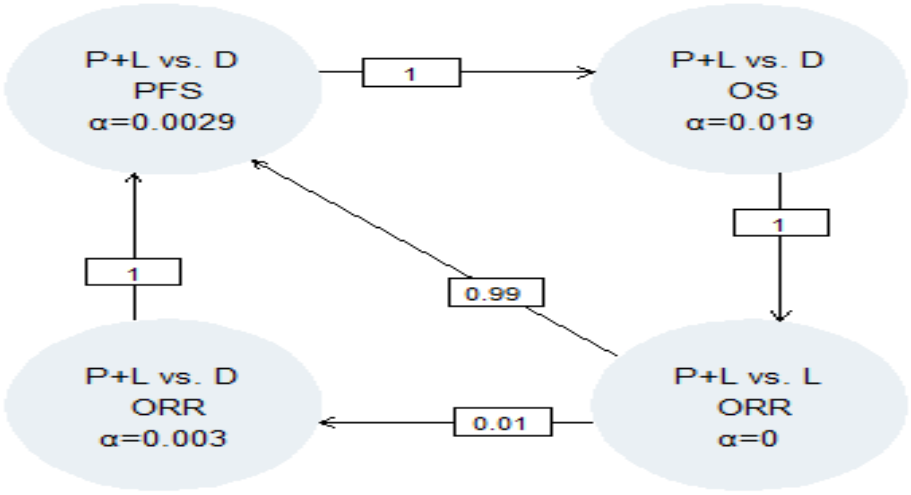
Abbreviations: IA1 = interim analysis 1; IA2 = interim analysis 2; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

9.8 Multiplicity

The study includes 1 single-arm futility analysis. A small α penalty of 0.0001 will be paid for looking at the data. The study will use the graphic method of Maurer and Bretz to control multiplicity for multiple hypotheses as well as IAs [Maurer, W. and Bretz, F. 2013]. The overall Type I error rate over the multiple endpoints will be controlled at 0.025 (1-sided). According to this approach, study hypotheses may be tested more than once, and, when a particular null hypothesis is rejected, the α allocated to that hypothesis can be reallocated to other hypothesis tests.

Figure 4 shows the initial 1-sided α 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.

Figure 4 Multiplicity Diagram for Type I Error Control



Abbreviations: P+L = pembrolizumab + lenvatinib arm. D = docetaxel arm. L = lenvatinib arm. ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

A small α penalty of 0.0001 is paid for futility analysis.

9.8.1 Objective Response Rate

9.8.1.1 Objective Response Rate – Pembrolizumab + Lenvatinib Versus Docetaxel

This study allocates α = 0.003 (1-sided) to compare ORR in pembrolizumab + lenvatinib to docetaxel, and ORR is tested only at the first interim analysis (IA1). However, if the test does not achieve statistical significance at IA1, the *p* value from IA1 can be compared to an updated α level if the null hypotheses for both PFS and OS are rejected and ORR in pembrolizumab + lenvatinib arm versus lenvatinib arm is rejected at a later time. Based on 200 randomized participants (in the pembrolizumab + lenvatinib and docetaxel arms) treated for at least 6 months, power and the approximate treatment difference required to reach the bound (ΔORR) are shown in Table 14, assuming 10% and 30% response rates in the docetaxel and pembrolizumab + lenvatinib arms, respectively.

Table 14 Possible Alpha Level and Approximate ORR Difference Between Pembrolizumab + Lenvatinib Arm and Docetaxel Arm Required to Demonstrate Efficacy for ORR at Interim Analysis 1

Alpha Level	~Δ Objective Response Rate	Power
0.003	~0.146	0.806
0.0249	~0.098	0.956

9.8.1.2 Objective Response Rate – Pembrolizumab + Lenvatinib Versus Lenvatinib

No initial alpha is allocated to compare ORR in pembrolizumab + lenvatinib versus lenvatinib and the ORR is tested only if the null hypothesis for OS is rejected at IA2 or the final analysis. If OS null hypothesis is rejected at IA2, alpha is fully reallocated to hypothesis testing for ORR in pembrolizumab + lenvatinib versus lenvatinib. If OS null hypothesis does not achieve statistical significance at IA2, the *p* value of ORR from IA2 can be compared to an updated α level if the null hypothesis for OS is rejected in the final analysis. Null hypothesis for ORR in pembrolizumab + lenvatinib versus lenvatinib may be tested at α = 0.019 (if OS null hypothesis is rejected, but not PFS null hypothesis), α = 0.0219 (if both OS and PFS null hypotheses are rejected, but not the null hypothesis for ORR in pembrolizumab + lenvatinib versus docetaxel), or α = 0.0249 (if all null hypotheses for PFS, OS and ORR in pembrolizumab + lenvatinib versus docetaxel are rejected). Based on 180 participants in pembrolizumab + lenvatinib arm and 45 participants in lenvatinib arm at IA2, the power and the approximate treatment difference required to reach the bound (ΔORR) are shown in Table 15, assuming 10% and 30% response rates in the lenvatinib and pembrolizumab + lenvatinib arms, respectively.

Table 15 Possible Alpha Level and Approximate ORR Difference Between Pembrolizumab + Lenvatinib and Lenvatinib Required to Demonstrate Efficacy for ORR

Alpha Level	~Δ Objective Response Rate	Power
0.019	~0.138	0.813
0.0219	~0.132	0.829
0.0249	~0.130	0.847

9.8.2 Progression-free Survival

This study allocates an α level of 0.0029 (1-sided) to test PFS, and PFS is tested only at IA2. Figure 4 shows that if the null hypothesis for ORR in pembrolizumab + lenvatinib versus docetaxel is rejected, α=0.003 is fully reallocated to PFS hypothesis testing. If the null hypothesis for OS is rejected and null hypothesis for ORR in pembrolizumab + lenvatinib versus lenvatinib is rejected with reallocated α level (α=0.019), then α=0.019 is essentially fully reallocated to PFS hypothesis testing. Thus, the PFS null hypothesis may be tested at α=0.0029, α=0.0059 (if the ORR in pembrolizumab + lenvatinib versus docetaxel null hypothesis is rejected), α=0.0219 (if the OS null hypothesis is rejected and ORR in pembrolizumab + lenvatinib versus lenvatinib null hypothesis is rejected, but not the ORR in pembrolizumab + lenvatinib versus docetaxel null hypothesis), or α=0.0249 (if OS null hypothesis and both the ORR null hypotheses are rejected). However, if the test of PFS does not achieve statistical significance at IA2, the *p* value of PFS from IA2 can be compared to an updated α level if the null hypotheses for OS is rejected and null hypothesis for ORR in pembrolizumab + lenvatinib versus lenvatinib from IA2 is rejected. Table 16 shows the bounds and boundary properties for PFS hypothesis testing for each of these α-levels. Note that the final row indicates the total power to reject the null hypothesis for PFS at each α-

level. If either ORR null hypothesis is rejected, PFS test may be compared to its updated bounds, considering the α reallocation from the 2 ORR hypotheses.

Table 16 Efficacy Boundaries and Properties for Progression-free Survival Analyses

Analysis	Value	α = 0.0029	α = 0.0059	α = 0.0219	α = 0.0249
IA2: 100% N = 360 Events: 279* Month: ~36	Z	2.7589	2.5181	2.0161	1.9618
	p (1-sided)[a]	0.0029	0.0059	0.0219	0.0249
	HR at bound[b]	0.7185	0.7396	0.7854	0.7906
	P(Cross) if HR=1[c]	0.0029	0.0059	0.0219	0.0249
	P(Cross) if HR=0.6[d]	0.9360	0.9610	0.9880	0.9896

Abbreviations: HR = hazard ratio; IA2 = interim analysis 2.
* Timing of IA2 is based on number of PFS events in Arm 1 and Arm 2 AND at least 6 months after the last participant is randomized.
[a] p (1-sided) is the nominal α for testing.
[b] HR at bound is the approximate HR required to reach an efficacy bound.
[c] P(Cross if HR=1) is the probability of crossing a bound under the null hypothesis.
[d] P(Cross if HR=0.6) is the probability of crossing a bound under the alternative hypothesis.

9.8.3 Overall Survival

OS is tested at IA2 and the final analysis. The OS hypothesis may be tested at α = 0.019 (initially allocated α), α = 0.0219 (if the PFS but not the ORR in pembrolizumab + lenvatinib versus docetaxel null hypothesis is rejected), or α = 0.0249 (if both the PFS and ORR in pembrolizumab + lenvatinib versus docetaxel null hypotheses are rejected).
Table 17 shows the bounds and boundary properties for OS hypothesis testing, derived using a Lan-DeMets O'Brien-Fleming spending function with α = 0.019, 0.0219, or 0.0249. If the actual number of OS events at the interim and final analyses differs from those specified in the table, the bounds will be adjusted using the Lan-DeMets O'Brien-Fleming spending function accordingly, with spending time determined by the minimum of the actual information fraction and the expected information fraction. For instance, if events accrue more slowly than expected or the same as expected, spending will be based on the actual information fraction. If events accrue more quickly than expected, cumulative spending based on the expected information fraction will be used, to save some α for analyses that will be performed with more than the originally planned maximum number of events. Also, note that if the PFS or ORR in pembrolizumab + lenvatinib versus docetaxel null hypothesis is rejected, each OS interim and final analysis test may be compared to its updated bounds, considering the α reallocation from the PFS or ORR hypothesis.

Table 17 Efficacy Boundaries and Properties for Overall Survival Analyses

Analysis	Value	α = 0.019	α = 0.0219	α = 0.0249
IA2: 80%[a] N = 360 Events: 240 Month: ~36	Z	2.3768	2.3120	2.2523
	p (1-sided)[b]	0.0087	0.0104	0.0122
	HR at bound[c]	0.7354	0.7415	0.7473
	P(Cross) if HR=1[d]	0.0087	0.0104	0.0122
	P(Cross) if HR=0.66[e]	0.8009	0.8183	0.8335
Final N: 360 Events: 299* Month: ~48	Z	2.1338	2.0780	2.0265
	p (1-sided)[b]	0.0164	0.0189	0.0214
	HR at bound[c]	0.7813	0.7863	0.7910
	P(Cross) if HR=1[d]	0.0190	0.0219	0.0249
	P(Cross) if HR=0.66[e]	0.9327	0.9398	0.9458

Abbreviations: HR = hazard ratio; IA2 = interim analysis 2.
* Timing of final analysis is based on number of OS events in Arm 1 and Arm 2 AND at least 12 months follow-up after the last participant is randomized.

[a] Percentage of expected number of events at final analysis anticipated at interim analysis.

[b] *p* (1-sided) is the nominal α for testing.

[c] HR at bound is the approximate HR required to reach an efficacy bound.

[d] P(Cross if HR=1) is the probability of crossing a bound under the null hypothesis.

[e] P(Cross if HR=0.66) is the probability of crossing a bound under the alternative hypothesis.

9.8.4 Safety Analyses

The eDMC has responsibility for assessment of the overall risk/benefit relationship. When prompted by safety concerns, the eDMC can request corresponding efficacy data. eDMC review of efficacy data to assess the overall ratio of risk/benefit to study participants will not require a multiplicity adjustment typically associated with a planned efficacy IA. However, to account for any multiplicity concerns raised by the eDMC review of unplanned efficacy data prompted by safety concerns, a sensitivity analysis for ORR, PFS, and OS, adopting a conservative multiplicity adjustment, will be prespecified in the sSAP.

9.9 Sample Size and Power Calculations

The study will randomize 405 participants in a 4:4:1 ratio into the pembrolizumab + lenvatinib, docetaxel, and lenvatinib arms. PFS and OS are primary endpoints for the study, with ORR and DOR as secondary endpoints. For the PFS endpoint, based on a target number of ~279 events at IA2 in 360 participants in pembrolizumab + lenvatinib and docetaxel arms the study has approximately 93.6% power to detect an HR of 0.6 at an overall α level of 0.29% (1-sided). For the OS endpoint, based on a target number of ~299 events in 360 participants in pembrolizumab + lenvatinib and docetaxel arms, with approximately 80% of the target number events at IA2, the study has approximately 93.3% power to detect an HR of 0.66 at an overall α level of 1.9% (1-sided). The above sample size and power calculations for PFS and OS assume the following:

- PFS follows an exponential distribution, with a median of 4.1 months for the docetaxel arm.
- OS follows an exponential distribution, with a median of 8.6 months for the docetaxel arm.
- The enrollment period is 30 months.
- The monthly drop-out rate is 2% and 0.17% for PFS and OS, respectively.
- The follow-up period is 18 months after the last participant is randomized.

The power calculations for ORR assume 10%, 10%, and 30% response rate in docetaxel, lenvatinib, and pembrolizumab + lenvatinib arms, respectively.

Based on 200 participants followed up for 6 months in pembrolizumab + lenvatinib and docetaxel arms at IA1, the power of ORR testing at the allocated $\alpha = 0.003$ is approximately 80.6% to detect a 20 percent point difference between an underlying 10% response rate in the docetaxel arm and a 30% response rate in the pembrolizumab + lenvatinib arm.

No initial alpha is allocated to compare ORR in pembrolizumab + lenvatinib versus lenvatinib and the ORR is tested only if the null hypotheses for OS is rejected at IA2 or final analysis.

Based on 180 participants in pembrolizumab + lenvatinib arm and 45 participants in lenvatinib arm at final analysis, the power of ORR testing at the allocated $\alpha = 0.019$ (reallocated from OS alpha) is approximately 81.3% to detect a 20 percent point difference between an underlying 10% response rate in the lenvatinib arm and a 30% response rate in the pembrolizumab + lenvatinib arm.

The sample size and power calculations were performed in R (“gsDesign” package) and with EAST 6.2.

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the between-group treatment effect (pembrolizumab + lenvatinib versus docetaxel) for OS, PFS, and ORR will be estimated and plotted by treatment arm within each category of the following classification variables:

- Stratification factors
  - Anti-PD-1/PD-L1 mAb (immediate prior therapy; not the immediate prior therapy)
  - TPS (<50%; ≥50%)
  - ECOG performance status (0;1)
- Histology (nonsquamous; squamous)
- Prior anti-PD-1/PD-L1 mAb (pembrolizumab as the only anti-PD-1/PD-L1 mAb [as monotherapy or combination therapy]); (other drug as the only anti-PD-1/PD-L1 mAb [as monotherapy or combination therapy])
- Age category (<65 years; ≥65 years)
- Sex (female; male)
- Smoking status (never; former/current smoker)
- Brain metastasis (present; absent)
- Liver metastasis (present; absent)
- Geographic region (east Asia; non-east Asia)

For subgroup analysis to take place, a given subgroup must include ≥10% of the total sample size in the two treatment arms to be compared.

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

Extent of exposure for a participant is defined as the number of cycles in which the participant receives the study intervention. Summary statistics will be provided on the 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)

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical

trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently 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 before 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 may be comprised of some or all of the following members:

- 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 EOC is composed of members of Sponsor Senior Management. The EOC will receive and decide on any recommendations made by the eDMC 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 eDMC 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 eDMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the eDMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7; Interim Analyses), and recommend to the EOC whether the study should continue in accordance with the protocol.

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the 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 trials 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 terminate the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP, or upon advice of the eDMC. If the eDMC makes a recommendation to alter the study conduct, it may be implemented by the Sponsor immediately upon EOC advice. In the event the Sponsor prematurely terminates a particular study or study site, the Sponsor will promptly notify the study site's investigators, health authorities, and IRB/IEC.

The DMC will recommend termination of the study if warranted, as described in Section 10.1.4.3. In addition, early study termination may occur based on clinical criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete;

2. Poor adherence to protocol and regulatory requirements;

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to participants;

4. Plans to modify or discontinue the development of the study drug.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests listed in Table 18 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 (see Appendix 7).
- Pregnancy testing:
    - Pregnancy testing requirements for study inclusion are described in Section 5.1.
    - Pregnancy testing (urine or serum) should be performed as required by local regulations during study treatment.
    - Pregnancy testing (urine or serum) should be performed as required by local regulations at the end of relevant systemic exposure and correspond with the time frame for female participant contraception in Section 5.1.
    - Additional urine or serum pregnancy tests may be performed, as determined necessary by the investigator or required by local regulations, to establish the absence of pregnancy at any time during the participant's participation in the study.

Table 18 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC indices: MCV[c] MCH[c] % reticulocytes[c]	WBC count with differential[a]: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	BUN[b]	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate[c]	Chloride[c]	Phosphorus[c]
	Creatinine[d]	Sodium	ALT/SGPT	Total protein[c]
	Glucose	Calcium	Alkaline phosphatase	Magnesium
	TSH	Free thyroxine[e]	Lactate dehydrogenase[c]	Amylase
	Lipase	Triiodothyronine (Total T3)[e]		
	Pregnancy test			

Laboratory Assessments	Parameters
Routine Urinalysis[f]	Specific gravity pH, glucose, protein[g], hemoglobin or blood, ketones by dipstick Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	PT/INR and aPTT/PTT[h] Serology (HIV RNA, HbsAg, and HCV antibody) Serum or urine β HCG pregnancy test (as needed for WOCBP)

Abbreviations: ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); β HCG = β human chorionic gonadotropin; BUN = blood urea nitrogen; C = Cycle; CO_2 = carbon dioxide; CPK = creatine phosphokinase; FSH = follicle stimulating hormone; FT3 = free triiodothyronine; FT4 = free thyroxine; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCV, mean corpuscular volume; PK = pharmacokinetic(s); PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cells; RNA = ribonucleic acid; SOC = standard of care; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; ULN = upper limit of normal; WBC = white blood cell; WOCBP = women of childbearing potential.

[a] Absolute or % acceptable per institutional standard.
[b] Urea is acceptable if BUN is not available as per institutional standard.
[c] Performed only if considered local standard of care.
[d] Glomerular filtration rate (GFR) (measured or calculated) or creatinine clearance can be used in place of creatinine.
[e] Free T4, total T3, and TSH levels will be determined during screening and then repeated on Day 1 of every other cycle (starting C2), at the time of discontinuation end of treatment), and at the safety follow-up visits. Free T3 is acceptable where total T3 cannot be determined. There may be instances when sites are unable to obtain thyroid function test results before scheduled dosing. After C1, review of thyroid function test results after dosing is acceptable.
[f] If urine dipstick testing suggests a urinary tract infection, or if clinically indicated, a urine microscopy, culture, and sensitivity should be performed at the institution's laboratory.
[g] If urine protein is ≥2+ (first occurrence or a subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level), then a 24-hour urine collection or an immediate spot urine protein-to-creatinine (UPCR) test should be done to quantify the 24-hour urine protein excretion. 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.
[h] Performed as part of the screening assessment and as clinically indicated for participants taking anticoagulants.

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

No laboratory results will be blinded, with the exception of PD-L1 TPS, to which investigators and participants will be blinded.

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention 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." Lenvatinib overdose without an associated AE is not reportable as an AE. Refer to Section 8.5 for the definition of overdose.

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 preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death
b. Is life-threatening
   - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization
   - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is

diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect
   - In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported on the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same time frame as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes..

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

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

- 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 CTCAE, version 4. 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 study intervention cause the AE?
- The determination of the likelihood that the study intervention 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 study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**
  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention 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 study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with IMP)?
  - **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 study intervention 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 study intervention; (3) the study is a single-dose drug study; or (4) study intervention (s) is/are only used 1 time.)
  - **Rechallenge:** Was the participant reexposed to the study intervention 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; (2) the study is a single-dose drug study; or (3) study intervention (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 STUDY INTERVENTION, OR IF REEXPOSURE TO THE STUDY INTERVENTION 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 IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention 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 their best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- 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 their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

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

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

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

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

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

Not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile 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 the 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

Contraceptives allowed during the study include[a]
Highly Effective 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] • Nonhormonal 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 in clinical studies. [b] If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable hormonal contraceptives are limited to those, which inhibit ovulation. [c] An 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).

10.5.3 Pregnancy Testing

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

Following initiation of study intervention, additional pregnancy testing will be performed as indicated in Section 1.3, during the treatment period and at least every 30 days up to at least 120 days after the last dose of pembrolizumab or lenvatinib or up to 30 days after the last dose of docetaxel, and as required locally.

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

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

Not applicable.

10.7 Appendix 7: Country-specific Requirements

10.7.1 Germany-specific Requirements

1. Exclusion Criterion 21: HIV testing is mandatory.

2. Exclusion Criterion 22: Hepatitis B and C testing is mandatory.

3. Exclusion Criterion 23: Tuberculosis testing is mandatory.

4. Section 6.6.3.1 (Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue): Participants should be discontinued from study treatment if any of the following AEs occur:

   - Stevens-Johnson syndrome

   - Toxic epidermal necrolysis

5. Please refer to the current pembrolizumab SmPC for additional guidance on management of immune-related AEs associated with pembrolizumab.

6. Please refer to the current lenvatinib SmPC for additional guidance on management of AEs associated with lenvatinib administration and other contraindications.

7. 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.

8. For participants to be eligible to participate in Germany, they must be capable of providing documented Informed Consent and Legally Acceptable Representative are not acceptable.

10.7.2 UK-specific Requirements

1. HIV, Hepatitis B and C testing is to be performed per local standards.

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

   Note: Any licensed COVID-19 vaccine (including for Emergency Use) is allowed in the study as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

10.7.3 Japan-specific Requirements

1. To assist early diagnosis of pneumonitis/interstitial lung disease (ILD) in study participants, the following parameters, including pulse oximetry monitoring (peripheral capillary oxygen saturation [SpO2]), C-reactive protein (CRP), KL-6, and surfactant protein D (SP-D) will be measured in this study. These parameters should be measured at the following times:

   - SpO2: at the time of vital sign assessment.

   - CRP, KL-6 and SP-D: at screening*, predose on Day 1 of every cycle, at the end of treatment, and at the safety follow-up visit (30 days after the last dose).

     *At the time of clinical laboratory tests, such as CBC and chemistry.

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

3. Section 6.1 (Study Intervention(s) Administered) Table 2 (Study Interventions): Pembrolizumab used in this study is categorized as “product(s) used in the clinical trial other than test product(s)” in Japan local regulation.

10.7.4 France-specific Requirements

Section 6.6.3.1 (Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue): Participants should be discontinued from study treatment if any of the following AEs occur:

- Stevens-Johnson syndrome
- Toxic epidermal necrolysis

Please refer to the current pembrolizumab SmPC for additional guidance on management of immune-related AEs associated with pembrolizumab.

Please refer to the current lenvatinib SmPC for additional guidance on management of AEs associated with lenvatinib administration and other contraindications.

10.7.5 Canada-specific Requirements

Section 6.6.2.9

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

10.7.6 Italy-specific Requirements

1. Section 6.6.3.1 (Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue): Participants should be discontinued from study treatment if any of the following AEs occur:

    - Stevens-Johnson syndrome
    - Toxic epidermal necrolysis

Please refer to the current pembrolizumab SmPC for additional guidance on management of immune-related AEs associated with pembrolizumab.

Please refer to the current lenvatinib SmPC for additional guidance on management of AEs associated with lenvatinib administration and other contraindications.

10.7.7 Portugal-specific Requirements

1. Exclusion Criterion 21: HIV testing is mandatory.

2. Exclusion Criterion 22: Hepatitis B and C testing is mandatory.

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

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic 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 radiologic PD by RECIST 1.1 as determined by the investigator, the investigator will decide whether to continue a participant on study intervention until repeat imaging is obtained (using iRECIST for participant management see Table 6 and Figure 3). This decision by the investigator should be based on the participant's overall clinical condition**.

**Clinical stability is defined as:

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

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

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

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

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir.
- **Note**: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of nontarget lesion(s) identified at baseline.
- Development of new lesion(s).

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

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

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

Assessment at Confirmatory Imaging

At confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iRECIST-confirmed stable disease [iSD]/iRECIST-confirmed partial response [iPR]/iRECIST-confirmed complete response [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 imaging for confirmation should be scheduled 4 to 8 weeks from the imaging at which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

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

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

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

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

Management Following Confirmatory Imaging

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

Note: If a participant has iCPD as defined above, but 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 imaging should continue to be performed following the intervals in the SoA (Section 1.3).

Detection of Progression at Visits After Pseudoprogression Resolves

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

- Target lesions
  - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudoprogression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudoprogression.
- Nontarget lesions
  - If nontarget lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If nontarget lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of nontarget lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time.
  - Additional new lesions appear.
  - Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum.
  - Previously identified nontarget lesions show any significant growth.

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

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

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

10.9 Appendix 9: Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry out all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.
5	Dead.
[Oken, M. M., et al 1982]	

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
1L	first-line
2L	second-line
ADA	antidrug antibodies
AE	adverse event
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase gene
ALT	alanine aminotransferase
APaT	all participants as treated
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
β-HCG	β human chorionic gonadotropin
BICR	blinded independent central review
BP	blood pressure
CI	confidence interval
CIV	central imaging vendor
COVID-19	Coronavirus Disease 2019
CR	complete response
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trials Facilitation and Coordination Group
CYP	cytochrome P450
DCR	disease control rate
DCR12	disease control rate at 12 weeks
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid

Abbreviation	Expanded Term
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDMC	external data monitoring committee
EEA	European Economic Area
EGFR	epithelial growth factor receptor
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC	European Organization for Research and Treatment of Cancer
ePRO	electronic patient-reported outcome
EQ-5D-5L	European Quality of Life Five-Dimensional Five-Level Questionnaire
EU CTR	European Union Clinical Trials Regulation
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act
FFPE	formalin-fixed, paraffin-embedded
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FoxP3	Forkhead box P3
FSH	follicle stimulating hormone
FT3	free triiodothyronine
FU	follow-up
GCP	Good Clinical Practice
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormone replacement therapy
IA	interim analysis

Abbreviation	Expanded Term
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCPD	iRECIST-confirmed progressive disease
iCR	iRECIST-confirmed complete response
iCRO	imaging contract research organization
IEC	Independent Ethics Committee
INR	international normalized ratio
iPR	iRECIST-confirmed partial response
irAE	immune-related AE
IRB	Institutional Review Board
iRECIST	Response Evaluation Criteria in Solid Tumors Version 1.1 for immune-based therapeutics
IRT	interactive response technology
iSD	iRECIST-confirmed stable disease
ITT	intention-to-treat
IUD	intrauterine device
iUPD	iRECIST-unconfirmed progressive disease
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
LFT	liver function tests
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MAPK	mitogen-activated protein kinase
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
ONJ	osteonecrosis of the jaw

Abbreviation	Expanded Term
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PDGF	platelet derived growth factor
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
Pgp	P-glycoprotein
PK	pharmacokinetic(s)
PO	oral(ly)
PopPK	population pharmacokinetics
PR	partial response
PRO	patient-reported outcome
Q3W	every 3 weeks
QD	once daily
QLQ-C30	Quality of Life Questionnaire Core 30 items
QLQ-LC13	Quality of Life Questionnaire Lung Cancer Module 13
QoL	quality of life
QTcF	QT interval corrected with Fridericia's formula
RCC	renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RNA	ribonucleic acid
ROS1	c-ros oncogene 1
RP2D	recommended Phase 2 dose
RTKi	receptor tyrosine kinase inhibitor
RUQ	right upper quadrant
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SGOT	serum glutamate oxaloacetate transaminase

Abbreviation	Expanded Term
SGPT	serum glutamate pyruvate transaminase
SoA	schedule of activities
SOC	standard of care
sSAP	supplemental statistical analysis plan
T3	triiodothyronine
T4	thyroxine
TAM	tumor-associated macrophage
TPS	tumor proportion score
TSH	thyroid-stimulating hormone
TTD	time to true deterioration
ULN	upper limit of normal
UPCR	urine protein/creatinine ratio
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of non-childbearing potential

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