Official Protocol Title:	A Phase 3, randomized, placebo-controlled, double-blind clinical study of pembrolizumab (MK-3475) with or without lenvatinib (E7080/MK-7902) to evaluate the safety and efficacy of pembrolizumab and lenvatinib as 1L intervention in a PD-L1 selected population of participants with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) (LEAP-010)
NCT number:	NCT05523323
Document Date:	16-Aug-2024

TITLE PAGE

THIS PROTOCOL AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME LLC, RAHWAY, NJ, USA (MSD).

Protocol Title: A Phase 3, randomized, placebo-controlled, double-blind clinical study of pembrolizumab (MK-3475) with or without lenvatinib (E7080/MK-7902) to evaluate the safety and efficacy of pembrolizumab and lenvatinib as 1L intervention in a PD-L1 selected population of participants with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) (LEAP-010).

Protocol Number: 010-06

Compound Number: MK-7902

Sponsor Name: Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)
This 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	04199104
EU CT	Not applicable
EudraCT	2019-003717-34
JAPIC-CT	Not applicable
WHO	Not applicable
UTN	Not applicable
IND	142277

Approval Date: 16 August 2024

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 06	16-AUG-2024	This change was made to address incorrect standard text. Language was inadvertently removed in the previous amendment.
Amendment 05	19-OCT-2023	The study is being terminated based on the results of an interim analysis, which showed a lack of clinical benefit on overall survival (OS) of the of the pembrolizumab plus lenvatinib combination over pembrolizumab monotherapy. This amendment serves to incorporate instructions for discontinuation of study intervention, appropriate measures for safety follow-up of ongoing study participants, and the plan for analysis of study data going forward.
Amendment 04	05-JUL-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Amendment 03	28-May-2021	Global amendment to update the dose modification and toxicity management guidelines for irAEs. The protocol was also updated to comply with lenvatinib label requirements for osteonecrosis of the jaw, NG/G tube update, and FDA commitment to update imaging language.
Amendment 02	03-JUN-2020	To incorporate Health Authority feedback received to date, modify the driver of IA2, amend exclusion criteria to allow administration of lenvatinib suspension through a gastrostomy tube, add nonemergency unblinding to guide further treatment decisions of participants with centrally-verified PD, remove iRECIST assessments, and provide program-level updates, corrections, and clarifications.
Amendment 01	25-OCT-2019	Removed anticoagulants, NSAIDS and aspirin from the list of prohibited medications within the Concomitant Therapy Section, as on-study use of anticoagulants, NSAIDS and aspirin are allowed.
Original Protocol	14-OCT-2019	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 06

Overall Rationale for the Amendment:

This change was made to provide correct language that was inadvertently removed in the previous amendment.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 10.3.5, Recording AE and SAE	Assessment of intensity/toxicity Inserted language to assist the investigator in assessing the intensity of AEs/SAEs in accordance with NCI CTCAE version 5. This guidance provides the definitions for Grade 1 through Grade 5 events.	This change was made to address incorrect standard text. Language was inadvertently removed in the previous amendment.

Section Number and Name	Description of Change	Brief Rationale
Other Changes in Amendment		
Section 1.1, Synopsis	Provided new language indicating that participants in China may continue in the trial until regulatory commitments have been met. The new language also provides guidance for participants in China to enroll into an extension study.	To clarify how discontinuation of participants in China will be addressed when all local regulatory commitments have been met.
Section 1.2, Schema	Expanded the introduction statement to include new language that participants in China may continue in the trial until regulatory commitments have been met. The new language also provides guidance for enrollment into an extension study.	Refer to Section 1.1 rationale.
	Removed language regarding extension study from Figure 3 and Figure 4 footnotes.	Deleted redundant information. Option for extension study is explained in Section 1.1 and in Section 6.8.
Section 6.7, Second Course	Inserted language stating that an OR or disease progression that occurs during the Second Course Phase will not be counted as an event for the primary analysis of in this study.	Refer to Section 10.3.5 primary reason rationale.
Section 7.3, Lost to Follow-up	Inserted language to help define participants who are considered lost to follow-up and the management of statistical data handling for these participants.	Refer to Section 10.3.5 (Assessment of intensity/toxicity) primary reason rationale.
Section 8.1.1, Informed Consent	Removed reference to FBR	FBR was not collected in this study.

Section Number and Name	Description of Change	Brief Rationale
Section 10.3.4, Additional Events Reported in the Same Manner as SAE	The section title and 1st paragraph were updated to provide consistent guidance in reporting AEs and SAEs.	Refer to Section 10.3.5 primary reason rationale (assessment of intensity/toxicity)
Section 10.3.5, Recording AE and SAE	Assessment of causality Inserted language to assist the investigator in identifying the cause of the AE/SAE and the use of specific components in assessing the relationship between the product and the AE.	Refer to Section 10.3.5 primary reason rationale (assessment of intensity/toxicity)
Sectio 10.7.2, China	Section 1.1 Synopsis and Section 1.2 Schema Provided new language indicating that participants in China may continue in the trial until regulatory commitments have been met. The new language also provides guidance for enrollment into an extension study.	Refer to Section 1.1 rationale.
Throughout	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, randomized, placebo-controlled, double-blind clinical study of pembrolizumab (MK-3475) with or without lenvatinib (E7080/MK-7902) to evaluate the safety and efficacy of pembrolizumab and lenvatinib as 1L intervention in a PD-L1 selected population of participants with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) (LEAP-010).

Short Title: A Phase 3 study of pembrolizumab (MK-3475) with or without lenvatinib (E7080/MK-7902) as 1L intervention in a PD-L1 selected population with R/M HNSCC (LEAP-010)

Acronym: LEAP-010

Hypotheses, Objectives, and Endpoints:

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

In males and females who are at least 18 years old, with a histologically confirmed diagnosis of R/M HNSCC that is biomarker positive (combined positive score (CPS ≥1)), and who are considered incurable by local therapies will be enrolled in this study.

Throughout this protocol, the term RECIST 1.1 refers to the adjustment of RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Refer to Section 4.2.1.1.1 for further details.

NOTE: Based on the data from an interim safety and efficacy analysis for LEAP-010 (data cutoff 30-MAY-2023), the study will be discontinued based on a lack of additional clinical benefit on overall survival (OS) of the combination of pembrolizumab plus lenvatinib over pembrolizumab monotherapy. At this interim analysis, the combination did not demonstrate an improvement in OS versus pembrolizumab alone, and the likelihood of reaching the protocol specified threshold for statistical significance for OS at a future analysis was evaluated and deemed to be low. Based upon these data, the study was unblinded on 16-AUG-2023. The prespecified third interim analysis and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further planned analyses for efficacy and ePRO endpoints.

NOTE: In alignment with the study-specific investigator letter dated 25-AUG-2023, all study participants still receiving pembrolizumab should continue to receive pembrolizumab monotherapy on study and undergo modified protocol study procedures as specified in this amendment. Study participation should end after the 30-day Safety Follow-up Visit (last scheduled visit) with the following exceptions: participants who are potential candidates for Second Course treatment will continue in Efficacy Follow-up and all participants in China will continue in Efficacy Follow-up and Survival Follow-up. All participants should stop ongoing treatment with lenvatinib/placebo.

Exceptions may be requested for lenvatinib for study participants who, in the assessment of their study physician, are benefiting from ongoing lenvatinib after consulting with the Sponsor. This applies to participants currently on pembrolizumab and lenvatinib and participants who have discontinued pembrolizumab and are currently continuing lenvatinib monotherapy. Participants who are considered by the investigator as candidates for continued monotherapy with lenvatinib after completion of 35 cycles of pembrolizumab and lenvatinib require a separate communication with the Sponsor. Participants who discontinue pembrolizumab prior to completion of Cycle 35 (eg, due to an AE) must discontinue lenvatinib at the same time.

All participants beyond the 30-day Safety Follow-up Visit (except participants who are potential candidates for Second Course treatment and all participants in China) should be discontinued from the study; however standard safety reporting should continue, as applicable. As of Amendment 05, participants who are still on study treatment will no longer require ePRO assessments or tumor response assessments by BICR to be performed. Scans will no longer be submitted to the iCRO. (Note: tumor response assessments by BICR and submission of scans to the iCRO will continue for participants in China.) Participants who are still on study medication should continue tumor imaging and investigator assessments of imaging per protocol. Biomarker specimen collection is discontinued. The 30-Day Safety Follow-up Visit is the last required visit (except for participants who are potential candidates for Second Course treatment and all participants in China). Updated analyses are described in Section 9. Participants in China will continue participation this trial until all regulatory commitments have been met. Upon completion of all regulatory requirements, participants in China are to be discontinued and may be enrolled in an extension study using pembrolizumab in combination with compound (eg, lenvatinib) if available.

Primary Objective	**Primary Endpoint**
Objective: To compare pembrolizumab + lenvatinib to pembrolizumab + placebo with respect to ORR per RECIST 1.1 as assessed by BICR. Hypothesis (H1): Pembrolizumab + lenvatinib is superior to pembrolizumab + placebo with respect to ORR per RECIST 1.1 by BICR.	OR, defined as a BOR of CR or PR
Objective: To compare pembrolizumab + lenvatinib to pembrolizumab + placebo with respect to PFS per RECIST 1.1 as assessed by BICR.	PFS, defined as the time from randomization to the first documented PD or death due to any cause, whichever occurs first.

Hypothesis (H2): Pembrolizumab + lenvatinib is superior to pembrolizumab + placebo with respect to PFS per RECIST 1.1 as assessed by BICR.	
Objective: To compare pembrolizumab + lenvatinib to pembrolizumab + placebo with respect to OS. Hypothesis (H3): Pembrolizumab + lenvatinib is superior to pembrolizumab + placebo with respect to OS.	OS, defined as the time from randomization to the date of death due to any cause.
Secondary Objectives	**Secondary Endpoints**
Objective: To evaluate pembrolizumab + lenvatinib and pembrolizumab + placebo with respect to DOR per RECIST 1.1 as assessed 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.
Objective: To assess the safety and tolerability of study intervention with pembrolizumab + lenvatinib and pembrolizumab + placebo.	-AEs -Study drug discontinuations due to AEs.

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Head and neck cancer metastatic Treatment of participants with R/M HNSCC
Population	Participants with R/M HNSCC (CPS ≥1) who are eligible for 1L treatment
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	Placebo

Study Blinding	Double-blind
Blinding Roles	Investigator Participants or Subjects Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 60 months 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 500 participants will be randomized. Randomization will be stratified according to: PD-L1 tumor expression as determined by PD-L1 IHC (TPS <50% vs. ≥50%); HPV status for oropharynx cancer as determined by p16 IHC (positive vs. negative); and ECOG performance status (0 vs. 1). All randomized participants are included in the ITT analysis as described in Section 9. After enrollment of the global portion of the study is complete, the study may remain open to enrollment in China alone until the target number of participants in China has been enrolled to meet local regulatory requirements.

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	Lenvatinib	10 mg 4 mg	20 mg	Oral	QD, no treatment duration limit	Test Product
Arm 1	Pembrolizumab	25 mg/mL	200 mg	IV Infusion	Day 1 of each 21-day cycle	Test Product
Arm 2	Matching placebo	N/A	N/A	Oral	QD, no treatment duration limit	Placebo
Arm 2	Pembrolizumab	25 mg/mL	200 mg	IV Infusion	Day 1 of each 21-day cycle	Test Product

EEA = European Economic Area; IMP = investigational medicinal product; IV = intravenous; N/A – not applicable; NIMP/AxMP = noninvestigational/auxiliary medicinal product; 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.

4mg capsules provided for successive dose reduction of lenvatinib, if needed, as described in Section 6.6.2.

Other current or former name(s) or alias(es) for study intervention(s) are as follows: KEYTRUDA®, MK-3475, SCH 900475; LENVIMA®, MK-7902, and E7080.

Total Number of Intervention Groups/Arms	2
Duration of Participation	Each participant will participate in the study from the time the participant provides documented informed consent through the final protocol-specified contact. After a screening phase of up to 42 days, each participant will be assigned to receive study intervention until disease progression is verified by BICR, unacceptable adverse events, intercurrent illness that prevents further administration of study treatment, investigator's decision to discontinue the participant, or administrative reasons requiring cessation of treatment. All participants receiving pembrolizumab will discontinue treatment with pembrolizumab after receiving 35 administrations. Participants who stop pembrolizumab after 35 administrations for reasons other than disease progression or intolerability or participants who stop pembrolizumab after attaining a Complete Response may be eligible for up to 17 additional administrations of pembrolizumab upon experiencing BICR-verified disease progression (Section 6.7). Participants who are receiving lenvatinib/placebo at the time disease progression is verified may continue to receive lenvatinib/placebo during Second Course treatment at the discretion of the investigator. Participants who discontinue lenvatinib/placebo prior to initiation of Second Course treatment will not restart lenvatinib/placebo. After the end of treatment, each participant will be followed for the occurrence of adverse events and spontaneously reported pregnancy as described under Section 8.4.

	Participants who discontinue for reasons other than radiographic disease progression will have post-treatment follow-up imaging for disease status until disease progression is documented per RECIST 1.1 by BICR, the start of a new anti-cancer treatment, withdrawal of consent, pregnancy, death, or loss to follow-up. All participants will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study. Upon study termination, participants are to be discontinued and may be enrolled in an extension study using pembrolizumab in combination with compound (e.g., lenvatinib) if available.

Study Governance Committees:

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

Study governance considerations are outlined in Appendix 1.

As of Amendment 05, the Executive Oversight Committee and Data Monitoring Committee are no longer applicable.

Study Accepts Healthy Participants: No

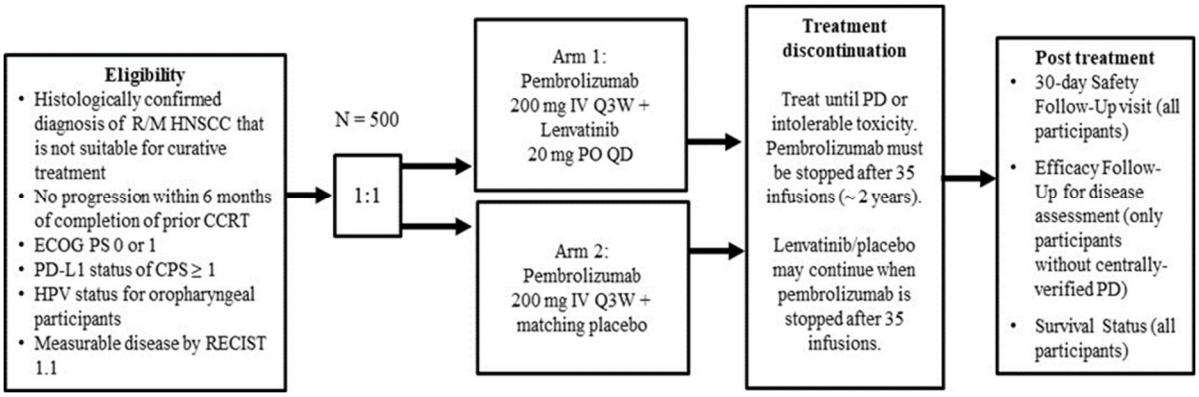
A list of abbreviations is in Appendix 10.

1.2 Schema

The original study design is depicted in Figure 1and Figure 2. The new study design per Amendment 05 is depicted in Figure 3 and Figure 4.

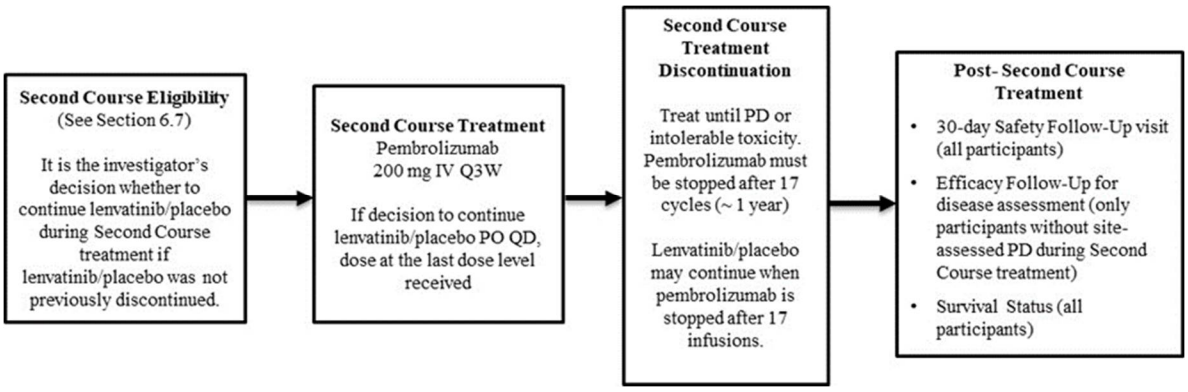
Participants in China will continue participation this trial until all regulatory commitments have been met. Upon completion of all regulatory requirements, participants in China are to be discontinued and may be enrolled in an extension study using pembrolizumab in combination with compound (eg, lenvatinib) if available. (See Appendix 7 for country-specific requirements.)

Figure 1 Original Study Design Initial Treatment Phase



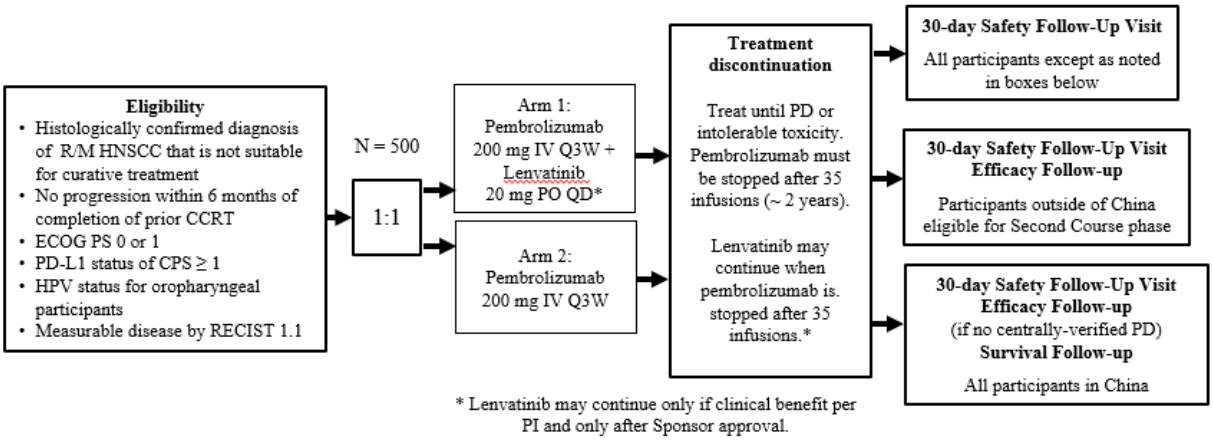
Abbreviations: CCRT = concomitant chemoradiotherapy; CPS = combined positive score; ECOG = Eastern Cooperative Oncology Group; HNSCC = head and neck squamous cell carcinoma; HPV = human papilloma virus; IV = intravenously; PD = progressive disease; PD-L1 = programmed cell-death-ligand 1; PO = orally; PS = performance status; Q3W = every 3 weeks; QD = daily; R/M = recurrent/metastatic; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors.

Figure 2 Original Study Design Second Course Phase



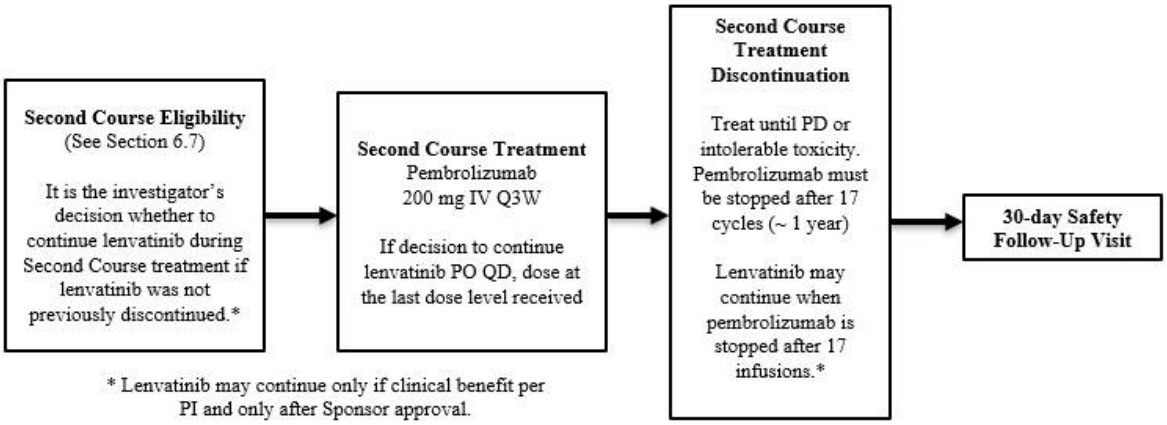
Abbreviations: IV = intravenously; PD = disease progression; PO = orally; Q3W = every 3 weeks; QD = daily.

Figure 3 New Study Design Initial Treatment Phase



Abbreviations: CCRT = concomitant chemoradiotherapy; CPS = combined positive score; ECOG = Eastern Cooperative Oncology Group; HNSCC = head and neck squamous cell carcinoma; HPV = human papilloma virus; IV = intravenously; PD = progressive disease; PD-L1 = programmed cell-death-ligand 1; PI = primary investigator; PO = orally; PS = performance status; Q3W = every 3 weeks; QD = daily; R/M = recurrent/metastatic; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors.

Figure 4 New Study Design Second Course Treatment Phase



Abbreviations: IV = intravenously; PD = disease progression; PI = primary investigator; PO = orally; Q3W = every 3 weeks; QD = daily.

1.3 Schedule of Activities

As of Amendment 05, participants who are still on study treatment will no longer require ePRO assessments to be performed. Biomarker samples (blood for genetic analysis, RNA analysis, plasma/serum biomarker analysis, ctDNA analysis and stool samples) are discontinued.

All participants who are still on study medication should continue tumor imaging and investigator assessments of imaging per protocol. Tumor response assessments by BICR will no longer be performed and scans will no longer be sent to the iCRO. Note: BICR assessments and submission of scans to the iCRO will continue for all participants in China.

Efficacy Follow-up visits will only be conducted for participants who are potential candidates for Second Course treatment and for all participants in China. Survival Follow-up Visits will only be conducted for participants in China.

Summary of changes in SoA:

- Imaging: while still on treatment and during efficacy follow-up as described above
- Physical Examination, Vital Signs: while still on treatment, then 30-day Safety FU
- ECG, MUGA or ECHO: while still on lenvatinib treatment then 30-day Safety FU
- Urinary laboratory tests, including 24-hour urine collection as specified per protocol: while still on lenvatinib treatment, then 30-day Safety FU
- Hematology/Chemistry: while still on treatment, then 30-day Safety FU
- T3, Free T4, TSH: while still on treatment, then 30-day Safety FU
- HIV, HBV, HCV: while still on treatment, then 30-day Safety FU
- ECOG: while still on treatment, then 30-day Safety FU

The full SoA tables below are retained for reference.

The SoAs for the Initial Treatment Phase and the Second Course Phase are provided in Table 1 and Table 2, respectively.

1.3.1 Initial Treatment Phase

Table 1 Initial Treatment Phase

Study Period:	**Screening**		**Intervention (21-Day Cycles)**										**Posttreatment Visits**			**Notes**
Visit Number/Title:	**1/Screening**		**C1**			**C2**		**C3**	**C4**	**C5**	**C6 to C35**	**≥ C36**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival FU**	
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**				
Scheduling Window (days)	**-42 to -1**	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**Approx 30d after last dose**	**Q6W (Y1) or Q9W (Y2+) (± 7d)**	**Q12W (± 14d)**	
Administrative Procedures																
Informed Consent	X															Additional consent is required if pembrolizumab is discontinued due to toxicity and participant will be receiving lenvatinib/placebo alone. Additional consent is required at disease progression if study treatment will continue and/or restart.
Inclusion/Exclusion Criteria		X														

Study Period:	**Screening**		**Intervention (21-Day Cycles)**										**Posttreatment Visits**			**Notes**
Visit Number/Title:	**1/Screening**		**C1**			**C2**		**C3**	**C4**	**C5**	**C6 to C35**	**≥ C36**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival FU**	
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**				
Scheduling Window (days)	**-42 to -1**	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**Approx 30d after last dose**	**Q6W (Y1) or Q9W (Y2+) (± 7d)**	**Q12W (± 14d)**	
Participant Identification Card		X	X													Identification card will be updated with randomization number.
Demographics and Medical History		X														Includes smoking and tobacco use.
Prior Treatment for HNSCC		X														
Prior/Concomitant Medication Review		X	X	X	X	X	X	X	X	X	X	X	X			
Randomization			X													It is strongly preferred that participants receive first dose of study intervention on day of randomization. Study intervention should begin within 3 days of randomization.

Study Period:	**Screening**		**Intervention (21-Day Cycles)**										**Posttreatment Visits**			**Notes**
Visit Number/Title:	**1/Screening**		**C1**			**C2**		**C3**	**C4**	**C5**	**C6 to C35**	**≥ C36**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival FU**	
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**				
Scheduling Window (days)	**-42 to -1**	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**Approx 30d after last dose**	**Q6W (Y1) or Q9W (Y2+) (± 7d)**	**Q12W (± 14d)**	
Subsequent Antineoplastic Therapy Status													X	X	X	
Survival Status			←									→			X	On Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Study Intervention Administration																
Lenvatinib/placebo Dispensing			X			X		X	X	X	X	X				
Lenvatinib/placebo Administration PO QD			←									→				Day 1 of each cycle dosed in clinic, 0-4 hours after pembrolizumab. Taken at home on all other days.
Lenvatinib/placebo container returned						X		X	X	X	X	X				

Study Period:	**Screening**		**Intervention (21-Day Cycles)**										**Posttreatment Visits**			**Notes**
Visit Number/Title:	**1/Screening**		**C1**			**C2**		**C3**	**C4**	**C5**	**C6 to C35**	**≥ C36**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival FU**	
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**				
Scheduling Window (days)	**-42 to -1**	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**Approx 30d after last dose**	**Q6W (Y1) or Q9W (Y2+) (± 7d)**	**Q12W (± 14d)**	
Pembrolizumab Administration IV Q3W			X			X		X	X	X	X					
Efficacy Procedure																
Tumor Imaging (head and neck, chest, abdomen) and RECIST Assessment Note: Imaging of the brain and pelvis are optional (if clinically indicated).		X						X		X	X	X		X		BICR confirmation of measurable disease is required at Screening. All imaging assessments will be calculated from the date of randomization. Imaging is performed at Screening, Week 6 (42 to 49 days) and every 6 weeks (± 7 days) during Year 1. After Year 1, imaging is performed every 9 weeks (± 7 days). This schedule will be maintained regardless of treatment delays.

Study Period:	**Screening**		**Intervention (21-Day Cycles)**										**Posttreatment Visits**			**Notes**
Visit Number/Title:	**1/Screening**		**C1**			**C2**		**C3**	**C4**	**C5**	**C6 to C35**	**≥ C36**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival FU**	
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**				
Scheduling Window (days)	**-42 to -1**	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**Approx 30d after last dose**	**Q6W (Y1) or Q9W (Y2+) (± 7d)**	**Q12W (± 14d)**	
Patient-reported Outcomes (PRO)																
EuroQoL EQ-5D-5L			X			X		X	X	X	X*		X	X			It is a best practice and strongly recommended that ePROs are administered before any other visit procedures and in the order listed in the SoA, starting with EuroQoL EQ-5D-5L. Collection begins at C1 and continues until C35 or treatment discontinuation, whichever occurs first. Specific Visit schedule is discussed in Section 8.2.2.
EORTC QLQ-C30			X			X		X	X	X	X*		X	X		
EORTC QLQ-H&N35			X			X		X	X	X	X*		X	X		

Study Period:	**Screening**		**Intervention (21-Day Cycles)**										**Posttreatment Visits**			**Notes**
Visit Number/Title:	**1/Screening**		**C1**			**C2**		**C3**	**C4**	**C5**	**C6 to C35**	**≥ C36**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival FU**	
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**				
Scheduling Window (days)	**-42 to -1**	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**Approx 30d after last dose**	**Q6W (Y1) or Q9W (Y2+) (± 7d)**	**Q12W (± 14d)**	
Safety Procedures																
AE/SAE Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Report AEs occurring within 30 days after the last dose of study intervention. Report SAEs occurring within 90 days after the last dose of study intervention, or 30 days after the last dose of study intervention if a new anticancer therapy is initiated, whichever is first.
Full Physical Examination		X											X			
Height		X														
Directed Physical Examination			X		X	X	X	X	X	X	X	X		X		

Study Period:	**Screening**		**Intervention (21-Day Cycles)**										**End of Treat-ment**	**Posttreatment Visits**			**Notes**
Visit Number/Title:	**1/Screening**		**C1**			**C2**		**C3**	**C4**	**C5**	**C6 to C35**	**≥ C36**		**Safety Follow-up**	**Efficacy Follow-up**	**Survival FU**	
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of treat-ment discon**	**Approx 30d after last dose**	**Q6W (Y1) or Q9W (Y2+) (± 7d)**	**Q12W (± 14d)**	
Contact				X													The investigator or medically qualified designee (consistent with local requirements) will assess participants for development of early toxicity. An unscheduled visit can occur before C1D15 if necessary for safety.

Study Period:	**Screening**		**Intervention (21-Day Cycles)**										**Posttreatment Visits**			**Notes**
Visit Number/Title:	**1/Screening**		**C1**			**C2**		**C3**	**C4**	**C5**	**C6 to C35**	**≥ C36**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival FU**	
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**				
Scheduling Window (days)	**-42 to -1**	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**Approx 30d after last dose**	**Q6W (Y1) or Q9W (Y2+) (± 7d)**	**Q12W (± 14d)**	
Vital Signs (resting BP, heart rate, RR, and temp) and weight		X	X		X	X	X	X	X	X	X	X	X	X		The Day 15 visit is mandatory for C1 and C2. During C3 and subsequent cycles, participants may return for the D15 visit if BP monitoring is required.

Study Period:	**Screening**		**Intervention (21-Day Cycles)**										**Posttreatment Visits**			**Notes**
Visit Number/Title:	**1/Screening**		**C1**			**C2**		**C3**	**C4**	**C5**	**C6 to C35**	**≥ C36**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival FU**	
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**				
Scheduling Window (days)	**-42 to -1**	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of treatment discon**	**Approx 30d after last dose**	**Q6W (Y1) or Q9W (Y2+) (± 7d)**	**Q12W (± 14d)**	
12-lead ECG with QTcF Determination		X	X			X					X	X	X	X			Every 4 cycles. ECG at Screening, C1D1, C2D1, D1 of every fourth cycle (12 weeks) thereafter (eg, C6, C10, C14, etc.), EOT, and safety follow-up. ECG at C1D1 and C2D1 should be performed approximately 2 hours post lenvatinib/placebo dose. For high-risk participants (Section 8.3.3), conduct ECG monitoring every cycle. If lenvatinib/placebo is discontinued, ECGs are only required at the EOT and Safety Follow-up visits.

Study Period:	**Screening**		**Intervention (21-Day Cycles)**										**Posttreatment Visits**			**Notes**
Visit Number/Title:	**1/Screening**		**C1**			**C2**		**C3**	**C4**	**C5**	**C6 to C35**	**≥ C36**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival FU**	
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**				
Scheduling Window (days)	**-42 to -1**	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**Approx 30d after last dose**	**Q6W (Y1) or Q9W (Y2+) (± 7d)**	**Q12W (± 14d)**	
MUGA Scan or ECHO		X											X			Additional LVEF assessments may be performed as clinically indicated.
ECOG Performance Status		X*	X			X		X	X	X	X	X	X	X		Performance status obtained on C1D1 before randomization may also be used as the screening value to determine eligibility. * Screening ECOG within 7 days before initiation of study intervention.

Study Period:	**Screening**		**Intervention (21-Day Cycles)**										**Posttreatment Visits**			**Notes**
Visit Number/Title:	**1/Screening**		**C1**			**C2**		**C3**	**C4**	**C5**	**C6 to C35**	**≥ C36**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival FU**	
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**				
Scheduling Window (days)	**-42 to -1**	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**Approx 30d after last dose**	**Q6W (Y1) or Q9W (Y2+) (± 7d)**	**Q12W (± 14d)**	
Laboratory Procedures/Assessments (Local Laboratory)																
Serum β-hCG or Urine Pregnancy Test (WOCBP only)		X				X		X	X	X	X	X	X	X		WOCBP require a negative test before randomization. If more than 24 hours have elapsed before the first dose of study intervention, another pregnancy test is required. A serum or urine pregnancy test will be performed per Appendix 2.
Serum FSH (WONCBP only)		X														In the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in postmenopausal range is required.

Study Period:	**Screening**		**Intervention (21-Day Cycles)**										**Posttreatment Visits**			**Notes**
Visit Number/Title:	**1/Screening**		**C1**			**C2**		**C3**	**C4**	**C5**	**C6 to C35**	**≥ C36**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival FU**	
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**				
Scheduling Window (days)	**-42 to -1**	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**Approx 30d after last dose**	**Q6W (Y1) or Q9W (Y2+) (± 7d)**	**Q12W (± 14d)**	
HIV, Hepatitis B, and Hepatitis C		X*														*Required at Screening only if mandated by local health authority
Hematology		X*			X	X		X	X	X	X	X	X			Labs obtained and reviewed on C1D1 before randomization may also be used as the screening value to determine eligibility. *Perform screening laboratory tests within 7 days before the first dose.
Chemistry		X*			X	X		X	X	X	X	X	X			

Study Period:	**Screening**		**Intervention (21-Day Cycles)**										**Posttreatment Visits**			**Notes**
Visit Number/Title:	**1/Screening**		**C1**			**C2**		**C3**	**C4**	**C5**	**C6 to C35**	**≥ C36**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival FU**	
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**				
Scheduling Window (days)	**-42 to -1**	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**Approx 30d after last dose**	**Q6W (Y1) or Q9W (Y2+) (± 7d)**	**Q12W (± 14d)**	
Thyroid Function Tests (T3 or FT3, Free T4, TSH)		X*				X			X		X	X	X			Labs obtained and reviewed on C1D1 before randomization may also be used as the screening value to determine eligibility. *Perform screening laboratory tests within 7 days before the first dose, then at C2 and every 2 cycles thereafter (C4, C6, C8, etc.).

Study Period:	**Screening**		**Intervention (21-Day Cycles)**										**Posttreatment Visits**			**Notes**
Visit Number/Title:	**1/Screening**		**C1**			**C2**		**C3**	**C4**	**C5**	**C6 to C35**	**≥ C36**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival FU**	
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**				
Scheduling Window (days)	**-42 to -1**	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**Approx 30d after last dose**	**Q6W (Y1) or Q9W (Y2+) (± 7d)**	**Q12W (± 14d)**	
Urine Dipstick Testing (or Urinalysis)		X*			X	X	X	X	X	X	X	X				After C1, collect samples at C1D15 and C2 D15 and up to 3 days before D1 of each cycle. If lenvatinib/ placebo is discontinued, urine dipstick testing no longer required. Urine dipstick testing (or urinalysis) obtained and reviewed on C1D1 before randomization may also be used as the screening value to determine eligibility. If 24-hour urine collection for quantitative assessment of proteinuria is required, randomization and C1D1 is postponed to after proteinuria result available.

Study Period:	**Screening**		**Intervention (21-Day Cycles)**										**Posttreatment Visits**			**Notes**
Visit Number/Title:	**1/Screening**		**C1**			**C2**		**C3**	**C4**	**C5**	**C6 to C35**	**≥ C36**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival FU**	
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**				
Scheduling Window (days)	**-42 to -1**	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**Approx 30d after last dose**	**Q6W (Y1) or Q9W (Y2+) (± 7d)**	**Q12W (± 14d)**	
																*Perform screening urinalysis tests within 7 days before the first dose.
Urinalysis		X*						X			X		X			Urinalysis obtained and reviewed on C1D1 before randomization may also be used as the screening value to determine eligibility. If 24-hour urine collection for quantitative assessment of proteinuria is required, randomization and C1D1 is postponed to after proteinuria result available. *Perform screening laboratory tests within 7 days before the first dose. Collect at C3, C6, C9, and every 3 cycles.

Study Period:	**Screening**		**Intervention (21-Day Cycles)**										**Posttreatment Visits**			**Notes**
Visit Number/Title:	**1/Screening**		**C1**			**C2**		**C3**	**C4**	**C5**	**C6 to C35**	**≥ C36**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival FU**	
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**				
Scheduling Window (days)	**-42 to -1**	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**Approx 30d after last dose**	**Q6W (Y1) or Q9W (Y2+) (± 7d)**	**Q12W (± 14d)**	
INR or PT and aPTT		X*														Labs obtained and reviewed on C1D1 before randomization may also be used as the screening value to determine eligibility. Additional testing is to be performed as clinically indicated for participants taking anticoagulants. *Perform screening laboratory tests within 7 days before the first dose.

Study Period:	**Screening**		**Intervention (21-Day Cycles)**										**End of Treat-ment**	**Posttreatment Visits**			**Notes**
Visit Number/Title:	**1/Screening**		**C1**			**C2**		**C3**	**C4**	**C5**	**C6 to C35**	**≥ C36**		**Safety Follow-up**	**Efficacy Follow-up**	**Survival FU**	
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of treat-ment discon**	**Approx 30d after last dose**	**Q6W (Y1) or Q9W (Y2+) (± 7d)**	**Q12W (± 14d)**	
HPV status using CINtec® p16 Histology assay (oropharynx participants only)		X															Historical result may be used. If historical result not available or testing cannot be completed locally, central laboratory can perform this test.
Biomarkers (Central Laboratory)																	
Newly Obtained or Archival Tumor Tissue Collection	X																PD-L1 results must be available from the central laboratory before randomization.
Blood for Genetic Analysis			X														Collect pre dose on C1D1.

Study Period:	**Screening**		**Intervention (21-Day Cycles)**										**Posttreatment Visits**			**Notes**
Visit Number/Title:	**1/Screening**		**C1**			**C2**		**C3**	**C4**	**C5**	**C6 to C35**	**≥ C36**	**End of Treat-ment**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival FU**	
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of treat-ment discon**	**Approx 30d after last dose**	**Q6W (Y1) or Q9W (Y2+) (± 7d)**	**Q12W (± 14d)**	
Blood for Plasma Biomarkers			X			X		X		X	X	X	X				Collect at pre dose on C1D1, C2D1, C3D1. After C3D1 collection, the plasma samples should be collected within ±7 days at subsequent imaging visits until EOT, including at the EOT visit.
Blood for Serum Biomarkers			X		X	X		X		X			X				Collect pre dose on C1D1, C1D15, C2D1, C3D1, C5D1 and at EOT.
Blood for RNA Analysis			X			X		X		X			X				Collect pre dose on C1D1, C2D1, C3D1, C5D1, and at EOT.

Study Period:	**Screening**		**Intervention (21-Day Cycles)**										**Posttreatment Visits**			**Notes**
Visit Number/Title:	**1/Screening**		**C1**			**C2**		**C3**	**C4**	**C5**	**C6 to C35**	**≥ C36**	**End of Treat-ment**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival FU**	
Cycle Day			**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**-42 to -1**	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of treat-ment discon**	**Approx 30d after last dose**	**Q6W (Y1) or Q9W (Y2+) (± 7d)**	**Q12W (± 14d)**	
Blood for Circulating Tumor Nucleic Acids			X			X		X		X	X	X	X				Collect at pre dose on C1D1, C2D1, C3D1. After C3D1 collection, the ctNA samples should be collected within ±7 days at subsequent imaging visits until EOT, including at the EOT visit.
Stool Analysis (Optional)			X			X				X			X				Pre dose (at home within 1 week before infusion) on C1D1, C2D1, C5D1 and at EOT.

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; BP = blood pressure; β-HCG; = β human chorionic gonadotropin; C = cycle; ctNA = circulating tumor nucleic acid; CXDY= Cycle X Day Y; d = day; discon = discontinuation; ePRO = electronic patient-reported outcome; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; 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; FU = follow-up; HIV = human immunodeficiency virus; HNSCC = head and neck squamous cell carcinoma; INR = international normalized ratio; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition; PRO = patient-reported outcome; PT = prothrombin time; Q6W = every 6 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; QLQ-C30 = Quality of Life Questionnaire Core 30 items; QTcF = QT interval corrected with Fridericia's formula; RNA= ribonucleic acid; RR = respiratory rate; SAE = serious adverse event; SoA = schedule of activities; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential; WONCBP = women of nonchildbearing potential.

1.3.2 Second Course Phase

Table 2 Second Course Phase

Study Period:	**Intervention (21-Day Cycles)**								**Posttreatment Visits**			**Notes**
Visit/Cycle Number	**C1**	**C2**	**C3**	**C4**	**C5**	**C6 to C17**	**≥ C18**	**End-of-Treatment**	**Safety Follow-up**	**Second Course Efficacy Follow-up**	**Survival FU**	
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of treatment discon**	**Approx. 30d after last dose**	**Q6W (± 7d)**	**Q12W (± 14d)**	
Administrative Procedures												
Informed Consent	X											Reconsent is required at the time of progression if study treatment will continue and/or restart.
Second Course Inclusion/Exclusion Criteria	X											
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X			
Subsequent Antineoplastic Therapy Status								X	X	X	X	
Survival Status	←						→				X	On Sponsor request, participants may be contacted for survival status at any time during the course of the study.

Study Period:	**Intervention (21-Day Cycles)**								**Posttreatment Visits**			**Notes**
Visit/Cycle Number	**C1**	**C2**	**C3**	**C4**	**C5**	**C6 to C17**	**≥ C18**	**End-of-Treatment**	**Safety Follow-up**	**Second Course Efficacy Follow-up**	**Survival FU**	
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of treatment discon**	**Approx. 30d after last dose**	**Q6W (± 7d)**	**Q12W (± 14d)**	
Study Intervention Administration												
Pembrolizumab Administration IV Q3W	X	X	X	X	X	X						
Lenvatinib/placebo Dispensing (Optional)	X	X	X	X	X	X	X					It is the investigator's decision whether to continue lenvatinib/placebo during Second Course treatment.
Lenvatinib/placebo Dosing PO QD (Optional)	←	—	—	—	—	—	→					It is the investigator's decision whether to continue lenvatinib/placebo during Second Course treatment.
Lenvatinib/placebo container returned		X	X	X	X	X	X	X				

Study Period:	Intervention (21-Day Cycles)							End-of-Treatment	Posttreatment Visits			Notes
Visit/Cycle Number	C1	C2	C3	C4	C5	C6 to C17	≥ C18		Safety Follow-up	Second Course Efficacy Follow-up	Survival FU	
Cycle Day	1	1	1	1	1	1	1					
Scheduling Window (days)	+3	±3	±3	±3	±3	±3	±3	At time of treatment discon	Approx. 30d after last dose	Q6W (± 7d)	Q12W (± 14d)	
Efficacy Procedures												
Tumor Imaging (head and neck, chest, abdomen) and RECIST Assessment Note: Imaging of the brain and pelvis are optional (if clinically indicated).	X*			X		X	X	X		X		*Baseline imaging is the CT or MRI showing centrally-verified PD. Baseline imaging should be performed within 28 days before C1. The first scan should be performed at 6 weeks (42 to 49 days) after restarting study intervention. Subsequent tumor scans are to be performed every 6 weeks (42 days [±7 days]) or more frequently, if clinically indicated. After 1 year (48 weeks), imaging will occur every 9 weeks (63 days ±7 days). This schedule will be followed regardless of delays in study intervention.

Study Period:	**Intervention (21-Day Cycles)**								**Posttreatment Visits**			**Notes**
Visit/Cycle Number	**C1**	**C2**	**C3**	**C4**	**C5**	**C6 to C17**	**≥ C18**	**End-of-Treatment**	**Safety Follow-up**	**Second Course Efficacy Follow-up**	**Survival FU**	
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of treatment discon**	**Approx. 30d after last dose**	**Q6W (± 7d)**	**Q12W (± 14d)**	
Safety Procedures												
AE/SAE Review	X	X	X	X	X	X	X	X	X	X		Report AEs occurring within 30 days after the last dose of study intervention. Report SAEs occurring within 90 days after the last dose of study intervention, or 30 days after the last dose of study intervention if a new anticancer therapy is initiated, whichever is first.
Full Physical Examination	X							X				
Directed Physical Examination		X	X	X	X	X	X		X			
Vital Signs (resting BP, heart rate, RR, and temp) and weight	X	X	X	X	X	X	X	X	X			

Study Period:	**Intervention (21-Day Cycles)**								**Posttreatment Visits**			**Notes**
Visit/Cycle Number	**C1**	**C2**	**C3**	**C4**	**C5**	**C6 to C17**	**≥ C18**	**End-of-Treatment**	**Safety Follow-up**	**Second Course Efficacy Follow-up**	**Survival FU**	
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of treatment discon**	**Approx. 30d after last dose**	**Q6W (± 7d)**	**Q12W (± 14d)**	
12-lead ECG with QTcF Determination (Only required for participants who receive lenvatinib/placebo in the Second Course treatment phase.)	X	X				X*		X	X			*D1 of every fourth cycle starting with C6. For high-risk participants (Section 8.3.3), conduct ECG monitoring every cycle. If lenvatinib/placebo is discontinued, ECG is only required at EOT and Safety FU visit.
ECOG Performance Status	X*	X	X	X	X	X	X	X	X			* Perform within 7 days before C1 of Second Course treatment.

Study Period:	**Intervention (21-Day Cycles)**							**End-of-Treatment**	**Posttreatment Visits**			**Notes**
Visit/Cycle Number	**C1**	**C2**	**C3**	**C4**	**C5**	**C6 to C17**	**≥ C18**		**Safety Follow-up**	**Second Course Efficacy Follow-up**	**Survival FU**	
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of treatment discon**	**Approx. 30d after last dose**	**Q6W (± 7d)**	**Q12W (± 14d)**	
Laboratory Procedures/Assessments (Local Laboratory)												
Pregnancy Test – urine or Serum β-hCG (WOCBP only) (Required on D1 of every cycle for participants who receive lenvatinib/placebo in the Second Course treatment phase.)	X*	X	X	X	X	X	X	X	X			*Obtain a urine pregnancy test within 24 hours before the first dose for all participants If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required. Additional urine/serum testing may be performed if clinically warranted, and/or as defined by local regulations.
Hematology	X*	X	X	X	X	X	X	X	X			*Perform within 7 days before first dose in C1 to confirm Second Course eligibility.
Chemistry	X*	X	X	X	X	X	X	X	X			
Thyroid Function Tests (T3 or FT3, Free T4, TSH)	X*		X		X	X	X		X			*Perform within 7 days before first dose in C1, then every 2 cycles thereafter (C3, C5, C7, etc.).

Study Period:	**Intervention (21-Day Cycles)**							**End-of-Treatment**	**Posttreatment Visits**			**Notes**
Visit/Cycle Number	**C1**	**C2**	**C3**	**C4**	**C5**	**C6 to C17**	**≥ C18**		**Safety Follow-up**	**Second Course Efficacy Follow-up**	**Survival FU**	
Cycle Day	**1**	**1**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At time of treatment discon**	**Approx. 30d after last dose**	**Q6W (± 7d)**	**Q12W (± 14d)**	
Urine Dipstick Testing (or Urinalysis; only required if participant is continuing to receive lenvatinib/placebo in Second Course)	X*	X	X	X	X	X	X		X			*Perform screening urinalysis test within 7 days before first dose in C1. Participants taking lenvatinib/placebo should have urine dipstick testing on Day 1 of each cycle.
Urinalysis (Only required after C1 if participant is continuing to receive lenvatinib/placebo in Second Course)	X*		X			X						Collect at C3, C6, C9, and every 3 cycles if participant is receiving lenvatinib/placebo. *Perform screening urinalysis tests within 7 days before first dose in C1 to confirm Second Course eligibility.
INR or PT and aPTT	X*											*Perform within 7 days before first dose in C1. Additional testing to be conducted as clinically indicated for participants taking anticoagulants.

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; β-HCG; = β human chorionic gonadotropin; C = cycle; CBC = complete blood count; CXDY= Cycle X Day Y ; D = day; discon = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end-of-treatment; FT3 = free triiodothyronine; FU = follow-up; INR = international normalized ratio; IV = intravenous; MRI = magnetic resonance imaging; PD = progressive disease; PT = prothrombin time; PTT = partial thromboplastin time; Q9W = every 9 weeks; Q12W = every 12 weeks; QTcF = QT interval corrected with Fridericia's formula; SAE = serious adverse event; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential.

2 INTRODUCTION

Pembrolizumab, a PD-1 inhibitor, in combination with lenvatinib, an anti-angiogenic tyrosine kinase inhibitor, are being investigated for participants eligible for 1L treatment of R/M HNSCC in this randomized, international, parallel design, double-blind, Phase 3 study.

2.1 Study Rationale

Head and neck cancers describe an anatomically heterogeneous group of cancers that arise most often from the oral cavity, the oropharynx, the hypopharynx, and the larynx [Dorsey, K. 2013]. More than 90% of head and neck cancers are squamous cell carcinomas, originating from the epithelium of the mucosal lining of the upper aerodigestive tract [Gupta, B., et al 2016]. Head and neck cancers are the ninth most common malignancy in the world with high mortality rates in developing countries (age-standardized mortality rates of 7.9 and 2.2 per 100,000 in males and females, respectively) [Gupta, B., et al 2016].

More than 90% of participants with HNSCC initially present with disease confined to the head and neck mucosa and/or to the regional cervical lymph nodes [Machiels, J. P. 2011]. Surgery and radiation therapy are markedly effective for participants with Stage I and II disease. However, despite intensive multimodal treatment, approximately 50% to 60% of participants with locally advanced Stage III or Stage IV HNSCC recur initially with locoregional disease. However, a significant proportion of these participants ultimately have incurable disease recurrence requiring palliative systemic treatment. The prognosis for participants with R/M HNSCC is dismal and OS is less than 1 year [Argiris, A., et al 2017].

Participants with R/M HNSCC present a therapeutic challenge. First-line treatment generally includes the combination of either cetuximab or docetaxel with a platinum-based chemotherapy with or without 5-FU. Participants who are asymptomatic usually are treated with monotherapy to balance the side-effects associated with combination regimens. Options for 1L single-agent treatment include platinum, 5-FU, paclitaxel, docetaxel, methotrexate, cetuximab, gemcitabine, or capecitabine [National Comprehensive Cancer Network 2018]. No Phase 3 randomized trial showed an improvement in OS for any regimen until the EXTREME trial [Vermorken, J. B., et al 2008]. This trial showed that the addition of cetuximab to the combination of platinum plus 5-FU improved median OS to 10.1 months from 7.4 months when compared with platinum plus 5-FU alone.

Data from the final analysis of KEYNOTE-048, an ongoing Phase 3, open-label trial to compare the efficacy and safety of pembrolizumab as monotherapy or in combination with chemotherapy (platinum plus 5-FU) versus the standard EXTREME chemotherapy regimen (cetuximab in combination with platinum plus 5-FU is provided in Section 2.2.3). In the population of all participants, there was a clinically meaningful difference in OS when comparing pembrolizumab plus chemotherapy with standard treatment. The pembrolizumab monotherapy group had more responders who achieved a CR and a more durable DOR.

In preclinical models, lenvatinib decreased the TAM population, which is known as an immune-regulator in the tumor microenvironment. By decreasing TAMs, expression levels of cytokines and immune-regulating receptors were changed to increase immune activation. The

immune-modulating effect of lenvatinib may result in a potent combination effect with PD-1/PD-L1 signal inhibitors. The effect of combining lenvatinib with anti-PD-1/PD-L1 agents has been investigated in the CT26 colorectal cancer syngeneic model (anti-PD-L1 agent) as well as the LL/2 lung cancer syngeneic model (anti-PD-1 agent). Combination treatment with lenvatinib and either an anti PD-1 or anti-PD-L1 agent showed significant and superior antitumor effects compared with either compound alone in these 2 syngeneic models [Kato, Y., et al 2015].

The ongoing pembrolizumab + lenvatinib combination Study 111/KEYNOTE-146 (Section 2.2.3) in participants with HNSCC has shown promising clinical activity and a manageable tolerability and safety profile [Taylor, M. H., et al 2018]. These results showed an ORR of 40.9% and median PFS of 8.2 months that strongly suggest greater efficacy with the combination of lenvatinib plus pembrolizumab than with either single agent, a possibly additive effect.

The intended population of this Phase 3 trial represents participants with a high unmet medical need considering all of the participants have incurable disease. Based on results from the KEYNOTE-048 trial, which compared pembrolizumab monotherapy to current standard platinum-based chemotherapy plus cetuximab, pembrolizumab monotherapy may be considered a new standard-of-care treatment in 1L R/M HNSCC participants whose tumors express PD-L1 (CPS ≥1). Combination therapy with pembrolizumab plus lenvatinib would provide additional 1L treatment options for HNSCC participants.

2.2 Background

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

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

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

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 Pembrolizumab

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

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are Type-I transmembrane glycoproteins containing an IgV–type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. After T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ, and ZAP70, which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in R/M HNSCC.

2.2.1.2 Lenvatinib

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

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

Lenvatinib inhibited cell free kinase activities for VEGFR1-3 and FGFR1-3 with Ki values around 1 nmol/L, and 8-22 nmol/L, respectively. In cell-based assays, lenvatinib inhibited VEGF-derived and FGF-derived tube formation of HUVEC with IC50 values of 2.1 and 7.3 nmol/L, respectively. Analysis of the signal transduction molecules revealed that lenvatinib inhibited both the MAPK pathway and the mTOR-S6K-S6 pathway in HUVECs triggered by

activated VEGFR and FGFR. Furthermore, lenvatinib (10, 30 mg/kg) significantly inhibited both VEGF- and FGF-driven angiogenesis in a murine in vivo model [Yamamoto, Y., et al 2014]. In vivo, lenvatinib exhibited antitumor activity against various human tumor xenografts in athymic mice including 5 types of thyroid carcinomas (differentiated [papillary and follicular], anaplastic, squamous, and medullary thyroid carcinomas), RCC, HCC, melanoma, gastric cancer, NSCLC, ovarian cancer, Ewing's sarcoma, and osteosarcoma. In addition, the antitumor activity of lenvatinib in combination with other anticancer agents in several xenograft models was greater than that of lenvatinib or the other agents alone.

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

2.2.1.3 Pembrolizumab Plus 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/L1 signal inhibitors. The effect of combining lenvatinib with an anti-human PD-1 humanized mAb was investigated in 4 murine tumor isograft models, which showed significant tumor growth inhibition compared to control. In the RAG murine tumor isograft tumor model, survival in the group treated with the combination was significantly longer than that of the respective monotherapy groups. In the CT26 murine tumor isograft model, treatment with the combination significantly increased the population of activated cytotoxic T cells compared to that of the respective monotherapy groups [Kato, Y., et al 2019]. All treatments were well tolerated and severe body weight loss was not observed.

2.2.2 Preclinical and Clinical Studies

2.2.2.1 Completed Studies With Pembrolizumab and Lenvatinib

Refer to the respective IBs for preclinical and clinical study data for pembrolizumab [IB Edition 17 2019] and lenvatinib [IB Edition 16 2019].

2.2.3 Ongoing Clinical Studies of Pembrolizumab and Lenvatinib

There is an expansive ongoing research program of clinical studies evaluating pembrolizumab in patients with a number of hematological and solid malignancies, including HNSCC. The clinical program for HNSCC consists of the completed and ongoing studies for recurrent/metastatic disease: KN012, KN055, KN040, and KN048, as well as this study, LEAP-010.

Lenvatinib is undergoing studies in participants with different types of solid tumors, including HNSCC, in combination with other therapies including PD-1 targeted therapies. Full lists of ongoing studies are in the respective IBs for pembrolizumab and lenvatinib.

Ongoing Clinical Studies of Pembrolizumab in HNSCC

KEYNOTE-012 (KN012)

KN012 is a Phase 1B, multicohort study evaluating the single-agent activity of pembrolizumab in various solid tumors, including 2 cohorts of participants (Cohorts B and B2) with R/M HNSCC. Cohort B consisted of 60 participants with PD-L1 positive HNSCC who received pembrolizumab 10 mg/kg Q2W. Cohort B2 consisted of 132 participants regardless of PD-L1 status, who received pembrolizumab 200 mg Q3W [Mehra, R., et al 2016]. Responses were seen in both HPV-positive and HPV-negative participants. This was the first immunotherapy demonstrating clinically meaningful antitumor activity in a heavily pretreated incurable HNSCC population with recurrent/metastatic disease. Enrollment is closed, but participants are ongoing in the study.

The efficacy and safety results after long-term follow-up based on pooled data from Cohorts B and B2 were presented at ASCO 2016 [Mehra, R., et al 2016]. In the recurrent/metastatic HNSCC population (n=192), the ORR was 21.9% (95% CI; 12.5% to 34.0%) in HPV-positive participants and 15.9% (95% CI: 10.0% to 23.4%) in HPV-negative participants. In a separate publication, when PD-L1 expression analyses were restricted to only tumor cells (tumor proportion scoring, TPS), there was no statistically significant increase ORR with PD-L1 positive (≥1%) versus negative (<1%) tumors. Conversely, when immune cells were included in the scoring system (CPS), PD-L1 expression on tumor and immune cells significantly correlated with ORR, PFS, and OS [Chow, L. Q., et al 2016]. Median OS was 8.5 months (95% CI: 6.5 to 10.5). The 6-month PFS rate was 24.9% [Mehra, R., et al 2016].

Importantly, the responses seen with pembrolizumab were durable. Among participants with recurrent/metastatic HNSCC, the DOR ranged from 1.8+ to 21.8+ months, and the median was not reached. Among participants who responded (n=34), 85% were in response for at least 6 months, and 71% of responders had ongoing responses [IB Edition 17 2019]. These

results show the consistent durability of responses seen with pembrolizumab treatment and compare favorably to SOC chemotherapy or epidermal growth factor receptor inhibitors.

These results of KN012 show consistent and clinically meaningful activity of pembrolizumab in heavily pretreated participants with HNSCC and show a robust and unprecedented antitumor activity observed compared with available current SOC chemotherapy agents. The prolonged DOR seen in the majority of participants that respond to pembrolizumab is substantially distinct from what is expected with chemotherapy in previously treated patients with HNSCC.

KEYNOTE-055 (KN055)

KN055 is a Phase 2, nonrandomized, single cohort study of pembrolizumab (200 mg Q3W) monotherapy in a heavily pretreated population of patients with recurrent/metastatic HNSCC who have progressed on prior platinum and cetuximab therapy. Results from 171 participants treated with pembrolizumab were presented by Bauml et al [Bauml, J., et al 2017]. When confirmed responses were evaluated, the ORR was 16% (CR, n=1; PR, n=27; 95% CI: 11% to 23%) with a median DOR of 8 months (range, 2+ to 12+ months); the stable disease rate was 19% (n=33; 95% CI: 14% to 26%). Response rates were slightly higher in participants that were PD-L1 positive; 18% of participants with CPS ≥1% PD-L1 expression responded to pembrolizumab compared with 12% of participants with CPS <1% expression. Nonetheless, PD-L1–negative participants responded to pembrolizumab at a rate that is clinically meaningful; 6- and 12-month PFS and OS rates were relatively similar between PD-L1–negative and PD-L1–positive participants. The results presented by Bauml et al [Bauml, J., et al 2017], confirm findings from KN012 in the recurrent/metastatic HNSCC population; pembrolizumab monotherapy (200 mg Q3W) demonstrates consistent and clinically meaningful activity in heavily pretreated participants with HNSCC.

KEYNOTE-040 (KN040)

KN040 is an ongoing Phase 3, randomized, active-controlled, open-label study of pembrolizumab versus the choice of 3 different SOC therapies in participants with R/M HNSCC. Four hundred and ninety-five participants with R/M HNSCC were randomized 1:1 to receive pembrolizumab 200 mg Q3W or the investigator's choice of one of the following therapies chosen before randomization: single agent methotrexate, single agent docetaxel, or single agent cetuximab. Randomization was stratified by ECOG performance status (0 vs. 1), HPV status (oropharynx – p16 positive vs. oropharynx – p16 negative or larynx/hypopharynx/oral cavity HNSCC), and PD-L1 status (strong positive or not; strong positive was defined as TPS ≥50% PD-L1 testing by IHC). The primary objective of the study was to evaluate OS in participants with R/M HNSCC treated with pembrolizumab compared with SOC treatment. Enrollment is closed, but participants are ongoing in the study.

The efficacy and safety data from the final analysis were reported, and at the time of the final analysis, 181 (73%) of 247 participants in the pembrolizumab group and 207 (83%) of 248 participants in the SOC group had died. The median OS in the ITT population was 8.4 months (95% CI 6.4 to 9.4) with pembrolizumab and 6.9 months (5.9 to 8.0) with SOC (HR

= 0.8, 0.65 to 0.98; nominal p=0.0161). In the ITT population, the median DOR was 18.4 months in the pembrolizumab group compared with only 5 months for SOC [Cohen, E. E. W., et al 2019].

For participants with a PD-L1 CPS≥1 tumor score, the HR for OS was 0.74 (95% CI 0.58 to 0.93; nominal p=0.0049), with a median survival of 8.7 months (95% CI 6.9 to 11.4) for pembrolizumab versus 7.1 months (5.7 to 8.3) with SOC. In participants whose tumor had PD-L1 TPS ≥50% expression, the HR for death was 0.53 (95% CI 0.35 to 0.81; nominal p=0.0014), and median OS was 11.6 months (95% CI 8.3 to 19.5) compared with 6.6 months (4.8 to 9.2) for pembrolizumab and SOC, respectively.

Fewer participants treated with pembrolizumab than with SOC had treatment-related AEs (63% vs. 84%), as well as higher toxicity AEs (Grade ≥3 treatment-related AEs 13% vs. 36%).

KEYNOTE-048 (KN048)

KN048 is an ongoing Phase 3, randomized, active-controlled, open-label study of pembrolizumab, or pembrolizumab plus platinum plus 5-FU chemotherapies versus platinum plus 5-FU plus cetuximab (EXTREME regimen) in participants with 1L R/M HNSCC. A total of 882 participants with 1L R/M HNSCC were randomized worldwide 1:1:1 between the 3 arms of the study to examine the efficacy and safety of pembrolizumab (n=301 participants), or pembrolizumab plus chemotherapy (n=281 participants) versus SOC with cetuximab and chemotherapy (n=300 participants) [Burtness, B., et al 2018] [CSR P048 2020]. The primary endpoints of the study are PFS per RECIST 1.1 as assessed by BICR, and OS. Participants are ongoing in the study [CSR P048 2020].

Data from the second interim analysis for KEYNOTE-048 were presented at the 2018 ESMO Congress [Burtness, B., et al 2018]. The cutoff date for this final PFS/interim OS analysis was13-JUN-2018, with a minimum follow-up of approximately 17 months. For OS, pembrolizumab monotherapy was superior to the EXTREME regimen in participants with a CPS ≥20, HR = 0.61 (95% CI 0.45-0.83, p=0.0007), and yielded a median OS that was longer with pembrolizumab (14.9 months) than the EXTREME regimen (10.7 months). Statistical significance was also achieved for pembrolizumab monotherapy in participants whose tumors had PD-L1 expression of CPS ≥1 with HR = 0.78 (95% CI 0.64 to 0.96, p=0.0086) and a median OS of 12.3 months versus 10.3 months in participants receiving the EXTREME regimen [Burtness, B., et al 2018].

Confirmed ORR for pembrolizumab versus EXTREME was 23% versus 36% for CPS ≥20 with a more durable DOR of 20.9 versus 4.2 months, and 19% versus 35% for CPS ≥1 with a median DOR of 20.9 versus 4.5 months for CPS ≥1 [Burtness, B., et al 2018].

Pembrolizumab monotherapy had a more favorable toxicity profile compared with the EXTREME regimen with few treatment-related AEs (58.3% vs. 96.9%), fewer treatment-related Grade 3 to 5 AEs (16.7% vs. 69.0%), and fewer treatment-related AEs that led to treatment discontinuation (4.7% vs. 19.9%) [CSR P048V01MK3475 2018].

Data cutoff of the final analysis was 25-FEB-2019 (approximately 25 months after the last participant was randomized) [CSR P048 2020]. In participants whose tumors had PD-L1 expression, OS results further confirmed the statistically and clinically meaningful results observed at the second interim analysis, with an OS HR = 0.74 (95% CI: 0.61, 0.90) for CPS ≥1 and HR = 0.58 (95% CI: 0.44, 0.78) for CPS ≥20 [CSR P048 2020]. In the population of all participants, there was a clinically meaningful difference in OS when comparing pembrolizumab plus chemotherapy with standard treatment. The pembrolizumab monotherapy group had more responders who achieved a complete response and a more durable DOR (22.6 vs. 4.5 months) [Rischin, D., et al 2019]. The safety results at the final analysis were similar to those observed at the second interim analysis.

At the second interim analysis, pembrolizumab + chemotherapy significantly improved OS in the total population (HR = 0.77 [95% CI 0.63-0.93]; p=0.00335) [CSR P048V01MK3475 2018]. Additionally, the safety profiles for pembrolizumab + chemotherapy and the EXTREME regimen were comparable (95.3% vs. 96.9% treatment-related AEs; 71.0% vs 69.0% treatment-related Grade 3 to 5 AEs; and 22.8% vs 19.9% treatment-related AEs that led to treatment discontinuation) [CSR P048V01MK3475 2018].

At the final analysis, pembrolizumab + chemotherapy OS results (HR = 0.72 [95% CI: 0.60, 0.87]) [CSR P048 2020] further confirmed the statistically significant and clinically meaningful OS observed at the second interim analysis. In the population of participants who tumors express PD-L1, OS was statistically significant and clinically meaningful in PD-L1 CPS ≥1 (HR = 0.65 [95% CI: 0.53, 0.80], p=0.00002) and in CPS ≥20 (HR = 0.60 [95% CI: 0.45, 0.82], p=0.00044) [CSR P048 2020]. Furthermore, in participants whose tumors had PD-L1 expression, ORR and median time to response were similar, but the pembrolizumab + chemotherapy group had more durable DOR of 6.7 versus 4.3 months for CPS ≥1 and 7.1 versus 4.2 months for CPS ≥20 [Rischin, D., et al 2019]. The safety results at the final analysis were similar to those observed at the second interim analysis.

In summary, for 1L R/M HNSCC, pembrolizumab monotherapy significantly improved OS over the EXTREME regimen in both the CPS ≥20 and CPS ≥1 populations. Responses to pembrolizumab were durable with a more favorable toxicity profile compared with the EXTREME regimen. Pembrolizumab plus chemotherapy improved OS in the total population and in participants whose tumors had PD-1 expression, with a comparable safety profile. Therefore, pembrolizumab-based treatment may be considered a new 1L standard of care for R/M HNSCC.

Study 111/KEYNOTE-146

Study 111/KEYNOTE-146 is a multicenter, open-label, Phase 1b/2 clinical study being conducted to evaluate the efficacy and safety of lenvatinib in combination with pembrolizumab in selected solid tumors (ie, HNSCC, NSCLC, RCC, endometrial cancer, urothelial carcinoma, and melanoma) [IB Edition 16 2019]. The Phase 1b portion of this study has been completed and Phase 2 is ongoing. During the Phase 1b portion of the study, the MTD was determined to be 20 mg lenvatinib daily 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.

As of 01-DEC-2017, 22 study participants with measurable, confirmed metastatic HNSCC and ECOG performance status of 0 or 1 were enrolled in this cohort and received lenvatinib (20 mg/day orally) + pembrolizumab (200 mg IV Q3W). Participants were not preselected based on PD-L1 status. Tumor assessments were performed by study investigators using irRECIST. Of the participants, 9.1% had received no prior anticancer therapy, 63.6% had received 1 prior line of anticancer therapy, and 13.6% had received 2 prior lines of anticancer therapies and 13.6% had received ≥3 prior lines of anticancer therapies, respectively. At data cutoff (01-DEC-2017), ORR was 40.9% (95% CI: 20.7, 63.6); ORR (at Week 24) was 36.4% (95% CI: 17.2, 59.3), including 1 (4.5%) CR, 8 (36.4%) PR, 11 (50%) SD, 0 (0%) PD, and 2 (9.1%) unknown; median PFS of 8.2 months (95% CI: 4.3, NE); and PFS rate at 12 months was 41.9 % (95% CI: 17.6, 64.7) [Taylor, M. H., et al 2018].

Grade 3 or 4 treatment-related AEs occurred in 72.7% of participants (Grade 3 treatment-related AEs in 15 participants [68.2%] and Grade 4 treatment-related AEs in 1 participant [4.5%]). The most common treatment-related AEs were fatigue (50.0%; Grade 3: 4.5%), hypertension (40.9%, Grade 3: 18.2%), and diarrhea (36.4%, Grade 3: 4.5%). Five participants experienced serious treatment-related AEs including hypertension, acute kidney injury, dehydration, hemoptysis and pulmonary edema. There were 5 fatal AEs reported; none were deemed treatment-related [Taylor, M. H., et al 2018].

Overall, the study showed promising clinical activity and manageable toxicities, supporting further evaluation of the lenvatinib + pembrolizumab in participants with HNSCC [Taylor, M. H., et al 2018a]. Interim analysis results for NSCLC, urothelial carcinoma, melanoma, endometrial carcinoma and RCC study arms produced similar response rates and acceptable safety and tolerability [Brose, M., et al 2018] [Vogelzang, N., et al 2018] [Taylor, M., et al 2018] [Makker, V., et al 2018] [Lee, C. H., et al 2018]. From these studies, the combination of pembrolizumab and lenvatinib showed promising clinical activity and a manageable safety profile that is consistent with the safety profile of each agent when administered as monotherapy.

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 results of the KEYNOTE-048 clinical trial demonstrating survival benefit with pembrolizumab for 1L R/M HNSCC, there is rationale for treating the participants with pembrolizumab monotherapy in the CPS ≥1 biomarker population. Therefore, pembrolizumab will be used in both the control and experimental arms, and all participants can be considered to be receiving clinically beneficial therapy. The existing data suggest that inhibiting angiogenesis in combination with PD-1 blockade is a promising therapeutic strategy, and the benefit/risk assessment for participants in this study is considered to be favorable, making the combination of pembrolizumab + lenvatinib a promising therapeutic

option to test in participants with 1L R/M HNSCC whose tumor demonstrates PD-L1 expression.

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

NOTE: Based on the data from an interim safety and efficacy analysis for LEAP-010 (data cutoff 30-MAY-2023), the study will be discontinued based on a lack of additional clinical benefit on OS of the combination of pembrolizumab plus lenvatinib over pembrolizumab monotherapy. At this interim analysis, the combination did not demonstrate an improvement in OS versus pembrolizumab alone, and the likelihood of reaching the protocol specified threshold for statistical significance for OS at a future analysis was evaluated and deemed to be low. Based upon these data, the study was unblinded on 16-AUG-2023. The prespecified third interim analysis and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further planned analyses for efficacy and ePRO endpoints.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

In males and females who are at least 18 years old, with a histologically confirmed diagnosis of R/M HNSCC that is biomarker positive (combined positive score (CPS ≥1)), and who are considered incurable by local therapies will be enrolled in this study.

Throughout this protocol, the term RECIST 1.1 refers to the adjustment of RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Refer to Section 4.2.1.1.1 for further details.

NOTE: Based on the data from an interim safety and efficacy analysis for LEAP-010 (data cutoff 30-MAY-2023), the study will be discontinued based on a lack of additional clinical benefit on OS of the combination of pembrolizumab plus; lenvatinib over pembrolizumab monotherapy. At this interim analysis, the combination did not demonstrate an improvement in OS versus pembrolizumab alone, and the likelihood of reaching the protocol specified threshold for statistical significance for OS at a future analysis was evaluated and deemed to be low. Based upon these data, the study was unblinded on 16-AUG-2023. The prespecified third interim analysis and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further planned analyses for efficacy and ePRO endpoints.

NOTE: In alignment with the study-specific investigator letter dated 25-AUG-2023, all study participants still receiving pembrolizumab should continue to receive pembrolizumab monotherapy on study and undergo modified protocol study procedures as specified in this amendment. Study participation should end after the 30-day Safety Follow-up Visit (last scheduled visit) with the following exceptions: participants who are potential candidates for Second Course treatment will continue in Efficacy Follow-up and all participants in China will continue in Efficacy Follow-up and Survival Follow-up. All participants should stop ongoing treatment with lenvatinib/placebo.

Exceptions may be requested for lenvatinib for study participants who, in the assessment of their study physician, are benefiting from ongoing lenvatinib after consulting with the Sponsor. This applies to participants currently on pembrolizumab and lenvatinib and participants who have discontinued pembrolizumab and are currently continuing lenvatinib monotherapy. Participants who are considered by the investigator as candidates for continued monotherapy with lenvatinib after completion of 35 cycles of pembrolizumab and lenvatinib require a separate communication with the Sponsor. Participants who discontinue pembrolizumab prior to completion of Cycle 35 (eg, due to an AE) must discontinue lenvatinib at the same time.

All participants beyond the 30-day Safety Follow-up Visit (except participants who are potential candidates for Second Course treatment and all participants in China) should be discontinued from the study; however standard safety reporting should continue, as applicable. As of Amendment 05, participants who are still on study treatment will no longer require ePRO assessments or tumor response assessments by BICR to be performed. Scans

will no longer be submitted to the iCRO. (Note: tumor response assessments by BICR and submission of scans to the iCRO will continue for participants in China.) Participants who are still on study medication should continue tumor imaging and investigator assessments of imaging per protocol. Biomarker specimen collection is discontinued. The 30-Day Safety Follow-up Visit is the last required visit (except participants who are potential candidates for Second Course treatment and all participants in China). Updated analyses are described in Section 9.

Primary Objective	**Primary Endpoint**
Objective: To compare pembrolizumab + lenvatinib to pembrolizumab + placebo with respect to ORR per RECIST 1.1 as assessed by BICR. Hypothesis (H1): Pembrolizumab + lenvatinib is superior to pembrolizumab + placebo with respect to ORR per RECIST 1.1 by BICR.	OR, defined as a BOR of CR or PR
Objective: To compare pembrolizumab + lenvatinib to pembrolizumab + placebo with respect to PFS per RECIST 1.1 as assessed by BICR. Hypothesis (H2): Pembrolizumab + lenvatinib is superior to pembrolizumab + placebo with respect to PFS per RECIST 1.1 as assessed by BICR.	PFS, defined as the time from randomization to the first documented PD or death due to any cause, whichever occurs first.
Objective: To compare pembrolizumab + lenvatinib to pembrolizumab + placebo with respect to OS. Hypothesis (H3): Pembrolizumab + lenvatinib is superior to pembrolizumab + placebo with respect to OS.	OS, defined as the time from randomization to the date of death due to any cause.

Secondary Objectives	**Secondary Endpoints**
Objective: To evaluate pembrolizumab + lenvatinib and pembrolizumab + placebo with respect to DOR per RECIST 1.1 as assessed 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.
Objective: To assess the safety and tolerability of study intervention with pembrolizumab + lenvatinib and pembrolizumab + placebo.	-AEs -Study drug discontinuations due to AEs.
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
Objective: To evaluate pembrolizumab + lenvatinib and pembrolizumab + placebo with respect to changes from baseline in HRQoL using the EORTC QLQ-C30 and EORTC QLQ-H&N35.	Scores from the EORTC QLQ-C30 and EORTC QLQ-H&N35. Global health status/quality of life and physical functioning scores of the EORTC QLQ-C30 will be evaluated as overall measures of HRQoL.
Objective: To evaluate pembrolizumab + lenvatinib and pembrolizumab + placebo with respect to health status as assessed using the EuroQoL EQ-5D-5L questionnaire, and to generate utility scores for use in economic models.	Health status and health utilities assessed using the EuroQoL EQ-5D-5L.
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 lenvatinib.	Molecular (genomic, metabolic, and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue.

4 STUDY DESIGN

4.1 Overall Design

Original protocol text that is contained in this section has been retained for reference.

NOTE: Based on the data from an interim safety and efficacy analysis for LEAP-010 (data cutoff 30-MAY-2023), the study will be discontinued based on a lack of additional clinical benefit on OS of the combination of pembrolizumab plus lenvatinib over pembrolizumab monotherapy. At this interim analysis, the combination did not demonstrate an improvement in OS versus pembrolizumab alone, and the likelihood of reaching the protocol specified threshold for statistical significance for OS at a future analysis was evaluated and deemed to be low. Based upon these data, the study was unblinded on 16-AUG-2023. The prespecified third interim analysis and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further planned analyses for efficacy and ePRO endpoints.

NOTE: In alignment with the study-specific investigator letter dated 25-AUG-2023, all study participants still receiving pembrolizumab should continue to receive pembrolizumab monotherapy on study and undergo modified protocol study procedures as specified in this amendment. Study participation should end after the 30-day Safety Follow-up Visit (last scheduled visit) with the following exceptions: participants who are potential candidates for Second Course treatment will continue in Efficacy Follow-up and all participants in China will continue in Efficacy follow-up and Survival Follow-up. All participants should stop ongoing treatment with lenvatinib/placebo.

Exceptions may be requested for lenvatinib for study participants who, in the assessment of their study physician, are benefiting from ongoing lenvatinib after consulting with the Sponsor. This applies to participants currently on pembrolizumab and lenvatinib and participants who have discontinued pembrolizumab and are currently continuing lenvatinib monotherapy. Participants who are considered by the investigator as candidates for continued monotherapy with lenvatinib after completion of 35 cycles of pembrolizumab and lenvatinib require a separate communication with the Sponsor. Participants who discontinue pembrolizumab prior to completion of Cycle 35 (eg, due to an AE) must discontinue lenvatinib at the same time.

All participants beyond the 30-day Safety Follow-up Visit (except participants who are potential candidates for Second Course treatment and all participants in China) should be discontinued from the study; however standard safety reporting should continue, as applicable. As of Amendment 05, participants who are still on study treatment will no longer require ePRO assessments or tumor response assessments by BICR to be performed. Scans will no longer be submitted to the iCRO. (Note: tumor response assessments by BICR and submission of scans to the iCRO will continue for participants in China.) Participants who are still on study medication should continue tumor imaging and investigator assessments of imaging per protocol. Biomarker specimen collection is discontinued. The 30-Day Safety Follow-up Visit is the last required visit (except participants who are potential candidates for

Second Course treatment and all participants in China). Updated analyses are described in Section 9.

This is a randomized, placebo-controlled, double-bind, parallel design, multisite study of pembrolizumab plus lenvatinib versus pembrolizumab plus placebo as 1L intervention in participants with R/M HNSCC whose tumors express PD-L1 (CPS ≥1). This Phase 3 study will be conducted in participants who have measurable disease per RECIST 1.1 as assessed by BICR, an ECOG performance status of 0 or 1, and have tumors that express PD-L1 CPS >1 by immunohistochemistry testing.

The original study design is shown in Figure 1 (Initial Treatment) and Figure 2 (Second Course). The new study design per Amendment 05 is depicted in Figure 3 and Figure 4.

Approximately 500 participants will be randomized 1:1 to Arm 1 (pembrolizumab + lenvatinib) or Arm 2 (pembrolizumab + placebo). Stratification factors for this study are:

- PD-L1 tumor expression as determined by PD-L1 immunohistochemistry (TPS <50% vs. ≥50%)
- HPV status for oropharynx cancer as determined by p16 immunohistochemistry (positive or negative); HPV status for participants without oropharynx cancer (eg, cancers of the oral cavity, hypopharynx and larynx) is considered HPV negative.
- ECOG performance status (0 vs. 1)

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.

Participants will be evaluated with radiographic imaging to assess response to study intervention every 6 weeks from randomization through Year 1, and every 9 weeks after Year 1. All imaging obtained during the study will be submitted to the iCRO for determination of ORR and PFS (Section 4.2.1.1.1). Tumor imaging showing site-assessed PD will be submitted for verification by BICR. Treatment beyond centrally-verified PD per RECIST 1.1 may be permitted at the discretion of the investigator after consultation with the Sponsor and receiving signed informed consent.

Survival follow-up will begin after centrally-verified PD (or on completion of all efficacy assessments if the participant is receiving study intervention beyond centrally-verified PD) or the start of new anticancer treatment, whichever occurs first. On 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 NCI CTCAE v5.0.

Treatment with pembrolizumab will continue for up to 35 treatment cycles, or until a discontinuation criterion (Section 7.1) is met. Participants who stop pembrolizumab after

35 cycles may continue to receive lenvatinib/placebo until a discontinuation criterion (Section 7.1) is met.

Participants who meet the criteria outlined in Section 6.7 may be considered for Second Course treatment with up to 17 cycles of pembrolizumab with or without lenvatinib/placebo.

After enrollment of the global portion of the study is complete, the study may remain open to enrollment in China alone until the target number of participants in China has been enrolled to meet local regulatory requirements. An extension portion of the study will be identical to the global study, (eg, inclusion and exclusion criteria, study endpoints, primary and secondary objectives, and study procedures).

Note: At the time of writing Amendment 05, enrollment in the China extension has closed. Refer to Appendix 7 for country-specific requirements.

Three interim analyses are planned in this study (Section 9.7).

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

This study will use OS, ORR and PFS as primary endpoints. OS has been recognized as the gold standard for demonstration of superiority of a new antineoplastic therapy in randomized clinical trial. ORR and PFS are based on RECIST 1.1 criteria as assessed by BICR as the primary endpoints. ORR and PFS are acceptable measures of clinical benefit for a late-stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The use of BICR and RECIST 1.1 to assess ORR and PFS is typically considered acceptable by regulatory authorities. Images will be submitted to an iCRO and read by an independent central review blinded to treatment assignment to minimize bias in the response assessments. In addition, the final determination of radiologic progression will be based on the central assessment of progression, rather than a local site investigator/radiology assessment. Expedited verification of radiologic progression as determined by central review will be communicated to the site.

4.2.1.1.1 RECIST 1.1

RECIST 1.1 will be used by the BICR when assessing images for efficacy measures. Although original RECIST 1.1 publication recommends a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented an adjustment to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ, if a larger number of target lesions is needed to adequately represent the tumor burden. Refer to Section 8.2.1.5 for additional detail.

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 5.0.

4.2.1.3 Exploratory Endpoints

4.2.1.3.1 Rationale for Patient-reported Outcomes Endpoints

Changes in HRQoL using PRO assessments can provide important information on clinical benefit and are accepted clinical endpoints by health authorities. Participants will provide information regarding their HRQoL using the EORTC QLQ-C30 and EORTC QLQ-H&N35 PRO instruments. Health utilities will be evaluated using the EQ 5D-5L PRO instrument. These PROs assessments are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

The EORTC QLQ-C30 and EORTC QLQ-H&N35 are psychometrically and clinically validated instruments appropriate for assessing HRQoL in participants with HNSCC [Bjordal, K., et al 1994] [Bjordal, K., et al 2000]. These instruments have been widely used in Phase 3 studies of participants with R/M HNSCC [Mesia, R., et al 2010] [Machiels, J. P., et al 2015] [Harrington, K. J., et al 2017] [Cohen, E. E. W., et al 2018].

EORTC QLQ-C30

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

EORTC QLQ-H&N35

The EORTC QLQ-H&N35 is a disease-specific questionnaire developed to measure QoL in head and neck cancer. The EORTC QLQ-H&N35 consists of 7 multi-item scales (pain in the mouth, problems with swallowing, senses, speech, social eating, social contact, and sexuality), and 11 single-item scales (problems with teeth, mouth opening, dry mouth, sticky saliva, coughing, feeling ill, use of analgesics, use of nutritional supplements, use of feeding tube, weight gain, and weight loss) [Bjordal, K., et al 1994].

EuroQoL EQ-5D-5L

The EuroQoL EQ-5D-5L is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in health economic analyses [Rabin, R. and de Charro, F. 2001]. The 5 health state dimensions in the EQ-5D-5L include the

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

4.2.1.4 Pharmacokinetic Endpoints

No PK endpoints are planned for this study.

4.2.1.5 Pharmacodynamic Endpoints

No pharmacodynamic endpoints are planned for this study.

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

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

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

Genetic (DNA) analyses from tumor

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, microsatellite instability) contributing towards the development/progression of cancer and/or driving response to therapy. Key molecular changes of interest to immuno-oncology drug development include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a ‘hyper-

mutated' state) may generate neo-antigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Evaluation of molecular targets and signaling pathways including angiogenesis and/or 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 immunosorbent assay (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.

Biomarker research using stool

Landmark studies have demonstrated that the gut microbiome can shape anti-tumor immunity and responses to immune checkpoint blockade in mouse models, and that modulation of the gut microbiome may enhance responses to immune checkpoint blockade. This has also been studied in patients on immune checkpoint blockade (anti-CTLA-4 and anti-PD-1), with evidence that differential bacterial signatures exist in responders versus non-responders to therapy (with responders having higher diversity of the gut microbiome and differential composition compared with non-responders). Importantly, these differences in the gut microbiome are associated with differential immune signatures in the tumor microenvironment [Lynch, S. V. 2016].

4.2.2 Rationale for the Use of Comparator/Placebo

Based on results from the KEYNOTE-048 trial, which compared pembrolizumab monotherapy to current standard platinum-based chemotherapy plus cetuximab, pembrolizumab monotherapy showed clinical benefit and may be considered a standard-of-care treatment in first-line R/M HNSCC participants whose tumors express PD-L1 (CPS ≥1) and is therefore being used as the comparator in this trial.

The use of a placebo in combination with pembrolizumab will ensure the objectivity of the local investigators' treatment decisions and AE causality assessments.

4.3 Justification for Dose

4.3.1 Pembrolizumab

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

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W representing an approximate 5- to 7.5-fold exposure range (refer to IB, Section 5.2.2)
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from PBPK analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment-naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q3W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies showed flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

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

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

4.3.2 Lenvatinib

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

Based on review of all of the clinical data from these 13 participants, the MTD and RP2D were determined to be 20 mg lenvatinib daily in combination with a fixed dose of 200 mg pembrolizumab given Q3W. Based on the promising anti-tumor efficacy and tolerable safety profile seen in both the endometrial carcinoma and RCC expansion cohorts from Study

111/KEYNOTE-146 [Makker, V., et al 2018], two 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.

4.3.3 Starting Dose for This Study

The starting dose of lenvatinib/placebo is 20 mg/day. Dose reductions of lenvatinib occur in succession based on the previous dose level (14, 10, and 8 mg/day). See Section 6.6 for dose modification. All participants will receive pembrolizumab 200 mg IV Q3W. Pembrolizumab dose reductions are not permitted.

4.3.4 Maximum Dose Exposure for This Study

NOTE: In alignment with the study-specific investigator letter dated 25-AUG-2023, all study participants still receiving pembrolizumab should continue to receive pembrolizumab monotherapy on study and undergo modified protocol study procedures as specified in this amendment. Study participation should end after the 30-day Safety Follow-up Visit (last scheduled visit) with the following exceptions: participants who are potential candidates for Second Course treatment will continue in Efficacy Follow-up and all participants in China will continue in Efficacy Follow-up and Survival Follow-up. All participants should stop ongoing treatment with lenvatinib/placebo.

Exceptions may be requested for lenvatinib for study participants who, in the assessment of their study physician, are benefiting from ongoing lenvatinib after consulting with the Sponsor. This applies to participants currently on pembrolizumab and lenvatinib and participants who have discontinued pembrolizumab and are currently continuing lenvatinib monotherapy. Participants who are considered by the investigator as candidates for continued monotherapy with lenvatinib after completion of 35 cycles of pembrolizumab and lenvatinib require a separate communication with the Sponsor. Participants who discontinue pembrolizumab prior to completion of Cycle 35 (eg, due to an AE) must discontinue lenvatinib at the same time.

The maximum dose/exposure of pembrolizumab allowed in this study is 200 mg Q3W for approximately 2 years (35 cycles). Participants meeting criteria for Second Course treatment with pembrolizumab (Section 6.7) may receive an additional 200 mg IV Q3W for up to 1 year (17 cycles).

The maximum dose/exposure of lenvatinib allowed in this study is 20 mg QD until disease progression or unacceptable toxicity.

4.4 Beginning and End-of-Study Definition

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

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped as described in Appendix 1.10.

5 STUDY POPULATION

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. Has histologically confirmed diagnosis of R/M HNSCC that is considered incurable by local therapies.

   Note: Participants with newly-diagnosed HNSCC must have distant metastases and be Stage M1 at study entry.
2. Has a primary tumor location of oropharynx, oral cavity, hypopharynx, or larynx.

   Note: Other primary tumor sites of HNSCC, including nasopharynx (any histology) or unknown primary tumor (including p16+ unknown primary) are not eligible.

Demographics

3. Is male or female, and at least 18 years of age at the time of documented informed consent.

Male Participants

Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

4. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 7 days after the last dose of lenvatinib/placebo

- 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.

  Please note that 7 days after lenvatinib is stopped, if the participant is on pembrolizumab only, no male contraception measures are needed.

Female Participants

Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

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

- Is not a WOCBP

  OR

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

Informed Consent

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

Additional Categories

7. Has measurable disease per RECIST 1.1 as assessed by BICR.

   Note: Lesions situated in a previously irradiated area are considered measurable if progression has been shown in such lesions.
8. Has provided an archival tumor tissue sample or newly obtained core, excisional, or incisional biopsy of a tumor lesion not previously irradiated. FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.

   Note: Details pertaining to tumor tissue submission can be found in the Procedures Manual.
9. Has a PD-L1 positive (CPS ≥1) tumor as determined by the central laboratory.
10. Participants with oropharyngeal cancer must have results from testing of HPV status defined as p16 IHC testing using CINtec® p16 Histology assay and a 70% cutoff point. If HPV status was previously tested using this method, no additional testing is required.

    Note: If local p16 testing results are not available or cannot be assessed using this method, a tumor tissue sample must be submitted for p16 testing at the designated central laboratory, and results must be received before randomization.
11. Has an ECOG performance score of 0 to 1.
12. Have adequately controlled BP with or without antihypertensive medications, defined as BP ≤150/90 mm Hg with no change in antihypertensive medications within 1 week prior to randomization.
13. Has adequate organ function as defined in the following table (Table 3). Specimens must be collected within 7 days before the start of study intervention.

Table 3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥30 mL/min for participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)[c]	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

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

b Creatinine clearance (CrCl) should be calculated per institutional standard.
Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

c PTT may be performed if the local lab is unable to perform aPTT.

5.2 Exclusion Criteria

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

Medical Conditions

1. Has any evidence of symptoms or signs of active tumor bleeding within 6 months before randomization.
2. Has radiographic evidence of major blood vessel invasion/infiltration or tumor demonstrates >90 degree abutment or encasement of a major blood vessel.

   Note: The degree of proximity to major blood vessels should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis after lenvatinib therapy.
3. Has a history of re-irradiation to any head and neck sites of disease including the cervical, infraclavicular or supraclavicular lymph nodes for head and neck cancer.
4. Has ulceration and/or fungation of disease onto the skin surface.

5. Has a life expectancy of less than 3 months and/or has rapidly progressing disease (eg, uncontrolled tumor pain) in the opinion of the treating investigator.
6. Has a history of any contraindication or has a severe hypersensitivity to any components of pembrolizumab (≥Grade 3) or lenvatinib.
7. Has pre-existing ≥Grade 3 gastrointestinal or non-gastrointestinal fistula.
8. Has a history of a gastrointestinal condition or procedure that, in the opinion of the investigator, may affect oral study drug absorption.
9. Has clinically significant cardiovascular impairment within 12 months of the first dose of study intervention, such as history of congestive heart failure greater than NYHA Class II, unstable angina, myocardial infarction or cerebrovascular accident/TIA/stroke, cardiac revascularization, or cardiac arrhythmia associated with hemodynamic instability.

   Note: Medically controlled arrhythmia that is stable with medication is permitted.
10. Has disease that is suitable for local therapy administered with curative intent.
11. Had PD within 6 months of completion of curatively intended systemic treatment for locoregionally advanced HNSCC.

    Note: Prior systemic therapy administered in the recurrent or metastatic setting is not permitted unless it was given as part of a multimodal treatment for locally advanced disease.
12. Has had major surgery within 3 weeks before first dose of study interventions.

    Note: Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility.
13. Has difficulty swallowing capsules or ingesting a suspension orally or by a feeding tube.

Prior/Concomitant Therapy

14. Has received prior therapy with lenvatinib or pembrolizumab.
15. Received last dose of systemic therapy for locoregionally advanced disease less than 6 months before signing consent.
16. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).
17. Has received prior systemic anticancer therapy including investigational agents within 4 weeks before randomization.

    Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible.
18. Has received prior radiotherapy within 2 weeks of start of study intervention.

    Note: Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.
19. Has received a live vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines is allowed.
    Refer to Section 6.5 for information on COVID-19 vaccines.

Prior/Concurrent Clinical Study Experience

20. Has Received an investigational agent or has used an investigational device within 4 weeks prior to study intervention administration.

Diagnostic Assessments

21. Has urine protein ≥1 g/24 hours.

    Note: Participants with proteinuria ≥2+ (≥100mg/dL) on urine dipstick testing (urinalysis) will undergo 24-hour urine collection for quantitative assessment of proteinuria.
22. Has prolongation of QTc interval (calculated using Fridericia's formula) to >480 msec.
23. Has a LVEF below the institutional (or local laboratory) normal range, as determined by MUGA or ECHO.
24. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study intervention.
25. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.

    Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
26. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, (ie, without evidence of progression) for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study intervention.
27. Has an active autoimmune disease that has required systemic treatment in past 2 years Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid) is allowed.
28. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
29. Has an active infection requiring systemic therapy (eg, tuberculosis, known viral or bacterial infections, etc.).
30. Has a known history of HIV infection.

    Note: No HIV testing is required unless mandated by local health authority.
31. Has a known history of hepatitis B (defined as HBsAg reactive) or known active hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

    Note: No testing for hepatitis B and hepatitis C is required unless mandated by local health authority.

32. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
33. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

Other Exclusions

34. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of study intervention.
35. Has had an allogenic 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.

5.4 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 CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

Clinical supplies (pembrolizumab and lenvatinib/matching placebo) will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

NOTE: In alignment with the study-specific investigator letter dated 25-AUG-2023, all study participants still receiving pembrolizumab should continue to receive pembrolizumab monotherapy on study and undergo modified protocol study procedures as specified in this amendment. Study participation should end after the 30-day Safety Follow-up Visit (last scheduled visit) with the following exceptions: participants who are potential candidates for Second Course treatment will continue in Efficacy Follow-up and all participants in China will continue in Efficacy Follow-up and Survival Follow-up. All participants should stop ongoing treatment with lenvatinib/placebo.

Exceptions may be requested for lenvatinib for study participants who, in the assessment of their study physician, are benefiting from ongoing lenvatinib after consulting with the Sponsor. This applies to participants currently on pembrolizumab and lenvatinib and participants who have discontinued pembrolizumab and are currently continuing lenvatinib monotherapy. Participants who are considered by the investigator as candidates for continued monotherapy with lenvatinib after completion of 35 cycles of pembrolizumab and lenvatinib require a separate communication with the Sponsor. Participants who discontinue pembrolizumab prior to completion of Cycle 35 (eg, due to an AE) must discontinue lenvatinib at the same time.

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

Country-specific requirements are noted in Appendix 7.

Table 4 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	Lenvatinib	Drug	Capsule	10 mg 4 mg	20 mg	Oral	QD, no treatment duration limit	Test Product	IMP	Central
Arm 1	Experimental	Pembrolizumab	Biological/Vaccine	Solution	25 mg/mL	200 mg	IV Infusion	Day 1 of each 21-day cycle	Test Product	IMP	Central
Arm 2	Experimental	Matching placebo	Drug	Capsule	N/A	N/A	Oral	QD, no treatment duration limit	Placebo	IMP	Central
Arm 2	Experimental	Pembrolizumab	Biological/Vaccine	Solution	25 mg/mL	200 mg	IV Infusion	Day 1 of each 21-day cycle	Test Product	IMP	Central

EEA = European Economic Area; IMP = investigational medicinal product; IV = intravenous; N/A = not applicable; NIMP/AxMP = noninvestigational/auxiliary medicinal product; 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.

4 mg capsules provided for successive dose reduction of lenvatinib, if needed, as described in Section 6.6.2.

All study interventions will be administered on an outpatient basis.

All products indicated in Table 4 will be provided centrally by the Sponsor or locally by the study site, subsidiary, or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the study site, subsidiary, or designee, every attempt will be made to source these supplies from a single lot/batch number. The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

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

6.1.1 Treatment

The initial treatment or first course of pembrolizumab Q3W consists of 35 treatments. Note: The number of treatments is calculated starting with the first dose.

These participants may be eligible for Second Course described in Section 6.7.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of pembrolizumab and lenvatinib/matching placebo are provided in the Pharmacy Manual.

Lenvatinib is provided as capsules for oral administration and does not require preparation. For participants unable to swallow capsules, a suspension can be prepared. Refer to the Pharmacy Manual for additional information.

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 randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to pembrolizumab + lenvatinib (Arm 1) or pembrolizumab + placebo (Arm 2) study interventions.

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

1. PD-L1 tumor expression as determined by PD-L1 immunohistochemistry (TPS <50% vs. ≥50%).
2. HPV status for oropharynx cancer as determined by p16 immunohistochemistry (positive vs. negative); HPV status for participants without oropharynx cancer (eg, cancers of the oral cavity, hypopharynx and larynx) is considered HPV negative.
3. ECOG performance status (0 vs. 1).

6.3.3 Blinding

After IA2, the study was unblinded on 16-AUG-2023. Original protocol text that is contained in this section has been retained for reference.

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

The treatment identity of pembrolizumab will be open-label; therefore, the Sponsor, investigator, and participant will know the intervention administered.

See Section 8.1.10 for the description of unblinding if a medical emergency occurs during the study.

6.4 Study Intervention Compliance

If there are interruptions in the study intervention schedule or infusion/injection was stopped, the details of and reason for any interruption or infusion/injection cessation of study intervention will be documented in the participant's medical record.

Interruptions from the protocol-specified treatment plan for ≥28 days for lenvatinib/placebo require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

Lenvatinib/placebo: On Day 1 of each cycle lenvatinib/placebo will be dosed in the clinic, 0 to 4 hours after pembrolizumab. Lenvatinib/placebo will be taken at home on all other days.

6.5 Concomitant Therapy

If there is a clinical indication for any medications or vaccinations prohibited, the investigator must discuss any questions regarding this with the Sponsor's Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator and the Sponsor.

The following medications and vaccinations are prohibited during the study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab and lenvatinib
- Radiation therapy
- Live or live-attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study.
  Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country 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.
- Refer to Appendix 7 for country-specific requirements.
- Systemic glucocorticoids except when used for the following purposes:
  - To modulate symptoms of an AE that is suspected to have an immunologic etiology
  - For the prevention of emesis
  - To premedicate for IV contrast allergies

  - To treat asthma or COPD exacerbations (only short-term oral or IV use in doses >10 mg/day prednisone equivalent)
  - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent
- Other glucocorticoid use except when used for the following purposes:
  - For topical use or ocular use
  - Intraarticular joint use
  - For inhalation in the management of asthma or COPD

If the investigator determines that a participant requires any of the following prohibited medications and vaccinations for any reason during the study, study intervention pembrolizumab+lenvatinib/placebo must be discontinued:

- Systemic antineoplastic chemotherapy, immunotherapy, or biological therapy not specified in this protocol
- Investigational agents other than those specified in this protocol
- Radiation therapy
- Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medications will be recorded on the eCRF including all prescriptions, OTC products, herbal supplements, and IV medications, and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

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

6.5.1 Rescue Medications and Supportive Care

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

Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6.2 for guidelines for lenvatinib/placebo dose modification and supportive care.

6.5.2 Drug Interactions

There are no DDI-related concomitant medication prohibitions or restrictions. Lenvatinib is not expected to clinically meaningfully alter exposure to CYP3A4/ P-glycoprotein (Pgp)

substrates based on results from a lenvatinib DDI study with midazolam (a sensitive CYP3A and Pgp substrate). Clinical studies also showed that co-administration of lenvatinib with either inducers or inhibitors of CYP3A4/Pgp are not of clinical concern.

No drug interaction is expected between pembrolizumab and lenvatinib because of their divergent metabolic pathways. Pembrolizumab is a mAb and is primarily catabolized like other proteins, while lenvatinib is metabolized by enzymatic (CYP3A and aldehyde oxidase) and nonenzymatic processes (LENVIMA® product information).

6.6 Dose Modification (Escalation/Titration/Other)

NOTE: In alignment with the study-specific investigator letter dated 25-AUG-2023, all study participants still receiving pembrolizumab should continue to receive pembrolizumab monotherapy on study and undergo modified protocol study procedures as specified in this amendment. Study participation should end after the 30-day Safety Follow-up Visit (last scheduled visit) with the following exceptions: participants who are potential candidates for Second Course treatment will continue in Efficacy Follow-up and all participants in China will continue in Efficacy Follow-up and Survival Follow-up. All participants should stop ongoing treatment with lenvatinib/placebo.

Exceptions may be requested for lenvatinib for study participants who, in the assessment of their study physician, are benefiting from ongoing lenvatinib after consulting with the Sponsor. This applies to participants currently on pembrolizumab and lenvatinib and participants who have discontinued pembrolizumab and are currently continuing lenvatinib monotherapy. Participants who are considered by the investigator as candidates for continued monotherapy with lenvatinib after completion of 35 cycles of pembrolizumab and lenvatinib require a separate communication with the Sponsor. Participants who discontinue pembrolizumab prior to completion of Cycle 35 (eg, due to an AE) must discontinue lenvatinib at the same time.

Adverse events will be graded using NCI CTCAE Version v5.0. Investigators will decide the probability of the event being related to one or both drugs as to whether dose modification of one or both drugs is required.

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

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

6.6.1 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.

Dose Modification and Toxicity Management Guidelines for irAEs Associated With Pembrolizumab Monotherapy, Coformulations, or IO Combinations are provided in Table 5.

Table 5 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated With Pembrolizumab Monotherapy, Coformulations, or IO Combinations

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

irAEs	Toxicity Grade (CTCAE v5.0)	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 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, or Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	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 to 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 or ALT Elevation or Increased Bilirubin	Grade 2[a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 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[b] or 4[c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations, or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hypothyroidism	Grade 2, 3, or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations, or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (which was previously myocarditis Grade 1 using CTCAE v4.0)	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		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event[e]		
	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] AST/ALT: >3.0 to 5.0 × ULN if baseline normal; >3.0 to 5.0 × baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 × ULN if baseline normal; >1.5 to 3.0 × baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 × ULN, if baseline normal; >5.0 to 20.0 × baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 × ULN if baseline normal; >3.0 to 10.0 × baseline if baseline abnormal

[c] AST/ALT: >20.0 × ULN, if baseline normal; >20.0 × baseline, if baseline abnormal; bilirubin: >10.0 × ULN if baseline normal; >10.0 × baseline if baseline abnormal

[d] 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.

[e] Events that require discontinuation include, but are not limited to encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis)

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reactions are provided in Table 6.

Table 6 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

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

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

CTCAE=Common Terminology Criteria for Adverse Events; h=hour; IV=intravenous; NCI=National Cancer Institute; NSAIDs=nonsteroidal anti-inflammatory drugs.
Note: Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.
For further information, please refer to the CTCAE v5.0 at http://ctep.cancer.gov

Other Allowed Dose Interruption for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical/surgical events or logistical reasons not related to study therapy. Participants should be placed back on 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.

6.6.2 Dose Modification with Lenvatinib

Lenvatinib dose reduction and interruption for participants who experience lenvatinib-pembrolizumab combination therapy-related toxicity will be in accordance with the dose modification guidelines described in Table 7. An interruption of study intervention for more than 28 days will require Sponsor approval before treatment can be resumed.

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

Refer to the subsections below for management of hypertension (Section 6.6.2.1), 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 7). For overlapping toxicities of pembrolizumab and lenvatinib/matching placebo, please refer to Section 6.6.3.

Table 7 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,f]		
First occurrence	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 14 mg once a day (1-level reduction)
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 10 mg once a day (1-level reduction)
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 8 mg orally once a day (1-level reduction)
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib	Discuss with Sponsor
Grade 4[g]: Discontinue Study Treatment		

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

Note: For grading see CTCAE version 5.0. Collect all AE grades (ie, decreasing and increasing CTCAE grade).

[a] An interruption of study treatment for more than 28 days will require Sponsor approval before treatment can be resumed.

[b] Initiate optimal medical management for nausea, vomiting, hypertension, hypothyroidism and/or diarrhea prior to any lenvatinib interruption or dose reduction.

[c] Applicable only to Grade 2 toxicities judged by the participant and/or physician to be intolerable.

[d] Obese participants (BMI ≥30) with weight loss do not need to return to their baseline weight or within 10% of their baseline weight (ie, Grade 1 weight loss). These participants may restart study intervention at a lower dose once their weight remains stable for at least 1 week and they have a minimum BMI of 25. The new stable weight should be used as the new baseline for further dose reductions.

[e] For asymptomatic laboratory abnormalities, such as Grade ≥3 elevations of amylase and lipase that are not considered clinically relevant by the investigator, continuation of treatment should be discussed with Sponsor.

[f] For Grade 3 thromboembolic event, permanently discontinue lenvatinib/matching placebo. See Section 6.6.2.5.

[g] Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

6.6.2.1 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 treatment with lenvatinib have BP of ≤150/90 mm Hg at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before C1D1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Regular assessment of BP should be as detailed in the SoA (Section 1.3.1 and Section 1.3.2). Hypertension will be graded using NCI CTCAE v5.0, based on BP measurements only (and not on the number of antihypertensive medications).

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

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

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

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

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

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

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

4. Institute appropriate medical management
5. Discontinue study drug

6.6.2.2 Management of Proteinuria

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

Detection and Confirmation

1. Perform urine dipstick testing or urinalysis per the SoA (Section 1.3). 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 UPCR test) is required in the following situations:
   - The first (initial) occurrence of ≥2+(≥100 mg/dL) proteinuria on urine dipstick (or urinalysis) while the participant is receiving lenvatinib.
   - A subsequent increase in severity of urine dipstick or urinalysis proteinuria occurring on the same lenvatinib dose level
   - When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is ≥2+ (≥100 mg/dL).
3. A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when UPCR is ≥2.4.

Grading of Proteinuria

- Grading according to NCI CTCAE v5.0 will be based on the 24-hour urinary protein result if one has been obtained. If the participant has 4+ proteinuria by dipstick (≥1000 mg/dL by urinalysis), a 24-hour urinary protein result is required to confirm Grade 3 proteinuria. Management of lenvatinib administration will be based on the grade of proteinuria according to Table 7.

Monitoring

- Urine dipstick or urinalysis testing for participants with proteinuria ≥2+ (≥100 mg/dL) should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ (30 mg/dL) or negative for 2 consecutive treatment cycles.
- Proteinuria monitoring can be performed at the local laboratory or investigator site, but must be managed by the site physician.
- In the event of nephrotic syndrome, lenvatinib must be discontinued.

6.6.2.3 Management of Diarrhea

An anti-diarrheal agent should be recommended to the participant at the start of study treatment, and participants should be instructed and educated to initiate anti-diarrheal treatment at the first onset of soft bowel movements. The choice of anti-diarrheal agent should be individualized to the participant's clinical circumstances and follow standard medical practice. If signs/symptoms of diarrhea persist despite optimal medical management, instructions contained in Table 7 should be followed.

6.6.2.4 Management of Hepatotoxicity

Liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) should be conducted as detailed in the SoA (Section 1.3.1 and Section 1.3.2) and as clinically indicated. If signs/symptoms indicating liver injury occur, instructions contained in Table 7 should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure (any grade per CTCAE v5) occurs, lenvatinib must be discontinued.

6.6.2.5 Management of Thromboembolic Events

Participants should be advised to pay attention to symptoms suggestive of venous thromboembolic events which include acute onset of shortness of breath, dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, DVT signs including lower-extremity swelling, and warmth to touch or tenderness. In case any of these symptoms appear, participants should be instructed to report such symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in Table 7 should be followed. Appropriate supportive care should be provided together with close monitoring. If a participant experiences a Grade 3 or a life threatening (Grade 4) thromboembolic reaction, including pulmonary embolism, lenvatinib/placebo must be discontinued.

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

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

Posterior Reversible Encephalopathy Syndrome/Reversible Encephalopathy Syndrome/ Reversible Posterior Leukoencephalopathy Syndrome (PRES/RPLS) is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. MRI is necessary to confirm the diagnosis of PRES/RPLS. Appropriate measures should be taken to control BP. In participants with signs or symptoms of PRES/RPLS, instructions in Table 7 should be followed.

6.6.2.7 Management of Hypocalcemia

Serum calcium should be monitored per the SoA (Section 1.3.1 and Section 1.3.2). Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v5.0, using the following formula:

Corrected calcium = ([4 – serum albumin in g/dL] × 0.8 + serum calcium)

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

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

6.6.2.8 Management of Hemorrhage

Instructions in Table 7 should be followed for the management of hemorrhage. Either resume at a reduced dose or discontinue lenvatinib depending on the severity and persistence of hemorrhage.

6.6.2.9 Management of Gastrointestinal Perforation or Fistula Formation

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

Refer to Appendix 7 for country-specific requirements.

6.6.2.10 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.

6.6.2.11 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 judgement of adequate resolution (See Section 6.6.4).

6.6.3 Dose Modifications for Overlapping Toxicities

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

1. Timing of AE onset
   Since lenvatinib is dosed daily and continuously due to a relatively short half-life (28 hours), and pembrolizumab is dosed Q3W due to a long half-life, lenvatinib can be

interrupted to assess whether an AE improves/resolves with dechallenge (ie, interruption of treatment) based on the following two scenarios:

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

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

2. Severity of AE
   If an AE is suspected to be treatment related and is severe/life threatening at the time of onset or is rapidly worsened, action including interrupting both drugs and initiating treatment with a corticosteroid (with exception of hypothyroidism, TIDM) and other supportive care should be taken promptly.
3. Participants receiving the combination therapy (pembrolizumab + lenvatinib) must discontinue study therapy if any of the following occur:
   - ALT or AST >5 X ULN for more than 2 weeks.
     Pembrolizumab will have already been permanently discontinued per Table 5, but lenvatinib may be administered at a reduced dose by the time this criterion is met and must be permanently discontinued immediately.
   - ALT or AST >3 X ULN and (TBL >2 X ULN or INR >1.5).
     Although Table 5 advises pembrolizumab to be withheld (interrupted), and Table 7 advises lenvatinib to have no dose modification or a reduction, if this criterion is met, both drugs must be permanently discontinued immediately.

6.6.4 Other Allowed Dose Interruptions

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

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

6.7 Second Course

All participants who stopped study intervention with SD or better may be eligible for up to an additional 17 cycles of pembrolizumab (approximately 1 year) if they progress after initial

treatment. This retreatment is the Second Course of this study, and a participant is eligible if the following conditions are met:

Either

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

OR

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

AND

- Experienced centrally-verified radiographic disease progression by RECIST 1.1 after stopping initial treatment, and
  - No new anticancer treatment was administered after the last dose of study intervention, and
  - The participant meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
  - The study is ongoing

As of Amendment 05: Participants will be considered for Second Course treatment upon investigator-assessed radiographic disease progression by RECIST 1.1. (Note: participants in China will be considered for Second Course after experiencing centrally-verified radiographic disease progression by RECIST 1.1.).

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

Participants who discontinue pembrolizumab after attaining CR or who complete treatment with pembrolizumab after 35 cycles will continue to receive lenvatinib/placebo alone until disease progression is verified by BICR, development of unacceptable toxicity, or withdrawal of consent. Participants who are receiving lenvatinib/placebo at the time disease progression is verified may continue to receive lenvatinib/placebo during Second Course treatment at the discretion of the investigator. Participants who discontinue lenvatinib/placebo before initiation of Second Course treatment will not restart lenvatinib/placebo.

6.8 Intervention After the End of the Study

Upon study termination, participants are to be discontinued and may be enrolled in an extension study using pembrolizumab in combination with compound (eg, lenvatinib) if available.

6.9 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity of lenvatinib or matching placebo. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). If the emergency unblinding call center is not available for a given site in this study, the central electronic intervention randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

6.10 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Original protocol text that is contained in this section and the following sections has been retained for reference.

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 before completion of the protocol-specified treatment period will still continue to be monitored in the study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.11.5 and 8.11.6 unless the participant has withdrawn from the study Section 7.2.

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.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Section 6.6.1, require Sponsor consultation prior to restarting treatment. If treatment will not be restarted, the participant will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- The participant has a positive urine drug screen at any time during the course of the study.
- Centrally-verified radiographic disease progression as outlined in Sections 8.2.1 and 8.2.1.5. Treatment beyond centrally-verified PD per RECIST 1.1 may be permitted at the discretion of the investigator and after consultation with the Sponsor and receiving signed informed consent.

- As of Amendment 05: Central tumor response assessments will no longer be performed. Participants who are receiving study intervention will be assessed locally by the investigator for disease progression per the protocol schedule. Scans will not be sent to the iCRO. (Note: participants in China will continue to have BICR tumor response assessments and will continue to submit scans to the iCRO.)
- Participants with RECIST 1.1 disease progression per local investigator assessment may continue pembrolizumab monotherapy at the discretion of the investigator and after consultation with the Sponsor and receiving signed informed consent.
- Participants with RECIST 1.1 disease progression must discontinue lenvatinib.

- Any progression or recurrence of malignancy, or any occurrence of another malignancy that requires active treatment.
- Recurrent Grade 2 pneumonitis
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Table 5, Table 6, or Table 7.
- Discontinuation of pembrolizumab may be considered for participants who have attained a confirmed CR and have been treated for at least 8 cycles (at least 24 weeks), receiving at least 2 doses of pembrolizumab beyond the date when the initial CR was declared. These participants may be eligible for Second Course treatment described in Section 6.7. Participants who stop pembrolizumab due to CR will continue to receive lenvatinib/placebo until PD verified by BICR or until a discontinuation criterion is met, if lenvatinib/placebo was not previously discontinued.

  As of Amendment 05: Participants who are considered by the investigator as candidates for continued monotherapy with lenvatinib after stopping pembrolizumab due to CR require a separate communication with the Sponsor.
- Completion of 35 treatments (approximately 2 years) with pembrolizumab

  Note: The number of treatments is calculated starting with the first dose. Participants who stop the combination or pembrolizumab after receiving 35 doses may be eligible for retreatment if they progress after stopping study intervention provided they meet the requirements detailed in Section 6.7. Participants receiving lenvatinib/placebo may continue to receive lenvatinib/placebo after completion of 35 treatments with pembrolizumab. Participants may be retreated in the Second Course Phase (Retreatment) for up to an additional 17 cycles (approximately 1 year) of pembrolizumab.

  As of Amendment 05: Participants who are considered by the investigator as candidates for continued monotherapy with lenvatinib after completion of 35 cycles of pembrolizumab and lenvatinib require a separate communication with the Sponsor.

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

ALT or AST elevation meeting the following criteria:

- ALT or AST >5 × ULN for more than 2 weeks
  Pembrolizumab will have already been permanently discontinued per Table 5, but lenvatinib may be administered at a reduced dose by the time this criterion is met and must be permanently discontinued immediately.
- ALT or AST >3 × ULN and (TBL >2X ULN or INR >1.5)
  Although Table 5 advises pembrolizumab to be withheld (interrupted), and Table 7 advises lenvatinib to have no dose modification or a reduction, if this criterion is met, both drugs must be permanently discontinued immediately.

7.2 Participant Withdrawal From the Study

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

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

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

7.3 Lost to Follow-up

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

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical (or dental) decisions must be made by an investigator who is a qualified physician (or dentist when appropriate).
- 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 used for screening or baseline purposes provided the procedures meet 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 Procedures Manual.

Repeat or unscheduled samples may be taken for safety reasons or for 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) 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 randomization, site personnel will add the treatment/randomization number to the participant identification card.

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

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically important. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

If a medical condition is diagnosed at the time of screening due to the physical examination, laboratory tests, radiologic assessment, other assessment, and/or a combination of these evaluations, the medical condition is to be recorded as a baseline condition along with the participant's other medical history unless due to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in).

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before the first dose of study intervention. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and will not be listed as a prior medication.

Medications taken 28 days before the first dose of Second Course study intervention will be recorded.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up Visit. Concomitant medications will be recorded for 30 days after the last dose of study intervention.

In addition, concomitant medications will be recorded during Second Course treatment, and for 30 days after the last dose of Second Course study intervention.

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 before randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a randomization number. The randomization number identifies the participant for all procedures occurring after

randomization. Once a randomization number is assigned to a participant, it can never be reassigned to another participant.

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

8.1.8 Study Intervention Administration

It is strongly preferred that participants receive the first dose of study intervention on the day of randomization. Study intervention should begin within 3 days of randomization.

Pembrolizumab: Study intervention(s) will be administered by the investigator and/or study staff according to the specifications within the pharmacy manual.

Lenvatinib/placebo: Lenvatinib/placebo will be administered by the investigator and/or study staff in the clinic on Day 1 of each cycle, 0 to 4 hours after pembrolizumab. All other lenvatinib/placebo doses will be taken at home. Lenvatinib/placebo will be administered according to the specifications in the Pharmacy Manual. An extemporaneous suspension of lenvatinib capsules should be used for participants unable to swallow capsules, as detailed in the Pharmacy Manual. Please refer to Section 8.1.8.1 for further details.

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 infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of – 5 minutes to +10 minutes is permitted (ie, infusion time is 30 minutes: –5 min/+10 min).

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

Lenvatinib/placebo: Lenvatinib 20 mg (two 10-mg capsules) or matching placebo will be taken orally with water (with or without food) once daily at approximately the same time each day in each 21-day cycle. Day 1 of each cycle will be dosed in the clinic, 0-4 hours after pembrolizumab.

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

Lenvatinib capsules should be swallowed whole. Alternatively, the capsules can be dissolved in a small glass of liquid (ie, water or apple juice) if a participant is unable to swallow or has a feeding tube. See the Pharmacy Manual for additional information.

8.1.8.2 Compliance

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 before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the End-of-Treatment visit 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

After efficacy IA2, the study was unblinded on 16-AUG-2023. Original protocol text that is contained in this section has been retained for reference.

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

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

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

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

<u>Nonemergency Unblinding</u>

After Sponsor consultation, participants may be unblinded if knowledge of treatment arm is required to guide future treatment decisions for the participant. Participants must have

centrally-verified PD and study intervention must be permanently discontinued for nonemergency unblinding to be considered.

For nonemergency unblinding (eg, after cases of centrally-verified PD and treatment discontinuation) IRT should be used to unblind the participant's treatment assignment. The emergency unblinding call center should not be used for this purpose.

Participants whose treatment assignment has been unblinded for any reason will continue to be monitored in the 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 Tumor Tissue for Biomarker Status

During the screening period, a tumor sample for each participant is required and is to be:

- A newly obtained core or incisional biopsy of a tumor lesion, which was not previously irradiated

Or

- An archival tumor tissue sample if a new biopsy is unavailable (depending on protocol requirements)

FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.

Details pertaining to tumor tissue submission can be found in the Procedures Manual.

The central laboratory will use the tissue sample to ascertain PD-L1 status using the PD-L1 IHC 22C3 pharmDx (Investigational Use Only) diagnostic kit. The diagnostic test is identical to the US FDA-approved PD-L1 IHC 22C3 pharmDx diagnostic kit except it is labeled IUO. The PD-L1 IHC 22C3 pharmDx assay kit is currently approved to select participants with HNSCC for treatment with pembrolizumab.

The PD-L1 CPS1 result will be unmasked to the site.

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

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

As of Amendment 05: Central tumor response assessments will be discontinued. Imaging scans will no longer be submitted to the iCRO nor read by BICR. Participants still on study intervention and participants in Efficacy Follow-up should continue tumor imaging and investigator assessments of imaging per protocol. (Note: participants in China will continue to have BICR tumor response assessments and will continue to submit scans to the iCRO.)

Original protocol text that is contained in this section has been retained for reference.

In addition to survival, efficacy will be assessed based on evaluation of scan changes in tumor burden over time, until the participant is discontinued from the study or goes into survival follow-up. The process for scan collection and transmission to the iCRO can be found in the SIM. Tumor scans by CT are strongly preferred. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. The same scan technique should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the response assessment based on scans.

Note: For the purposes of assessing tumor scans, the term "investigator" refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility.

If brain scans are performed, magnetic resonance imaging is preferred; however, CT imaging will be acceptable, if MRI is medically contraindicated.

Bone scans may be performed to evaluate bone metastases. Any supplemental scans performed to support a positive or negative bone scan, such as plain x-rays acquired for correlation, should also be submitted to the iCRO.

Expedited confirmation of measurable disease based on RECIST 1.1 by BICR at Screening will be used to determine participant eligibility. Confirmation by the BICR that the participant's imaging shows at least 1 lesion that is appropriate for selection as a target lesion per RECIST 1.1 is required before participant randomization.

All scheduled scans for participants will be submitted to the iCRO. In addition, a scan that is obtained at an unscheduled time point, for any reason (including suspicion of progression or other clinical reason), should also be submitted to the iCRO if it shows disease progression, or if it is used to support a response assessment. All scans acquired within the protocol-specified window of time around a scheduled scan visit are to be classified as pertaining to that visit.

When the investigator identifies radiographic progression per RECIST 1.1, the iCRO will verify this progression and email the results to the study site and Sponsor. In clinically stable participants, imaging should continue until PD has been verified by BICR (if initial site-assessed PD was not verified by BICR, each subsequent scan must be submitted to iCRO with verification of PD request until PD has been verified by BICR).

8.2.1.1 Initial Tumor Scans

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

The Screening scans must be submitted to the iCRO for confirmation of measurable disease per RECIST 1.1 for eligibility before randomization.

Tumor scan performed as part of routine clinical management is acceptable for use as screening tumor scan if it is of diagnostic quality and performed within 28 days before the date of randomization and can be assessed by the iCRO for confirmation of measurable disease.

If brain scans are required to document the stability of existing metastases, the brain scan should be acquired during screening. The specific methods permitted for this study are described in the SIM.

8.2.1.2 Tumor Scans During the Study

The first on-study scan should be performed at Week 6 (42 to 49 days window) from the date of randomization. Subsequent tumor scans should be performed every 6 weeks (42 days ± 7 days) or more frequently if clinically indicated. After 48 weeks, participants who remain on treatment will have scans performed every 9 weeks (63 days ± 7 days). Scan timing should follow calendar days and should not be adjusted for delays in cycle starts. Scans should continue to be performed until disease progression is identified by the investigator and verified by the BICR, the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first.

Treatment beyond centrally-verified PD per RECIST 1.1 may be permitted at the discretion of the investigator after consultation with the Sponsor and receiving signed informed consent. Participants who continue treatment beyond centrally-verified PD must continue tumor assessments as described in the SoA (Section 1.3.1). Investigator assessments are to be documented on the eCRF, but scans are not to be submitted to the iCRO. Further progression and discontinuation of study intervention are to be determined by the investigator.

Objective response should be confirmed by a repeat scan performed at least 4 weeks after the first indication of a response is observed. Participants will then return to the regular schedule scans, starting with the next scheduled scan time point. Participants who receive additional scan for confirmation do not need to undergo the next scheduled scan if it is fewer than 4 weeks later; scans may resume at the subsequent scheduled time point.

On-study brain scan should be performed if clinically indicated or to confirm CR (if other lesions indicate CR and brain lesions existed at baseline).

8.2.1.3 End-of-treatment and Follow-up Tumor Scans

As of Amendment 05: follow-up tumor imaging is only required for participants who are candidates for Second Course treatment. Imaging scans will no longer be submitted to the iCRO nor read by BICR. Original protocol text that is contained in this section has been retained for reference. (Note: participants in China will continue to have BICR tumor response assessments and will continue to submit scans to the iCRO.)

If participants discontinue study intervention without documented disease progression, every effort is to be made to monitor disease status by acquiring tumor scans using the same schedule calculated from the date of randomization, refer to Section 8.2.1.2.

Scans are to be continued until one of the following conditions are met:

- disease progression as defined by RECIST 1.1 verified by BICR
- the start of a new anticancer treatment
- pregnancy
- death
- withdrawal of consent
- the end of the study

8.2.1.4 Second Course (Retreatment) Tumor Scans

Tumor scans must be performed within 28 days before restarting study intervention with pembrolizumab.

If disease progression has been verified by BICR for the First Course, the Second Course may be initiated. The disease progression scan may be used as the Second Course baseline scan if performed within 4 weeks prior to dosing and meets scan standards.

The first scan should be performed at 6 weeks (42-49 days) after restarting study intervention. Subsequent tumor scans are to be performed every 6 weeks (42 days ±7 days) or more frequently, if clinically indicated. After 48 weeks, scans are to be performed every 9 weeks (±7 days) or more frequently, if clinically indicated.

Scans are to be performed until:

- disease progression
- the start of a new anticancer treatment
- withdrawal of consent

- death
- completion of Second Course
- or notification by the Sponsor, whichever occurs first

If participants discontinue study intervention, tumor scans are to be performed at discontinuation (±4-week window) unless previous scans were obtained within 4 weeks of discontinuation. If participants discontinue study intervention due to documented disease progression, this is the final required tumor scan.

If participants discontinue study intervention without documented disease progression, every effort is to be made to monitor disease status by acquiring tumor scans every 6 weeks (42 days [±7 days]) until the start of a new anticancer treatment, disease progression, death, or the end of the study, whichever occurs first.

8.2.1.5 RECIST 1.1 Assessment of Disease

As of Amendment 05: Central tumor response assessments will be discontinued. Imaging scans will no longer be submitted to the iCRO nor read by BICR. However, participants in China will continue to have BICR tumor response assessments and will continue to submit scans to the iCRO.

RECIST 1.1 will be used as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study intervention). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

Upon investigator-assessed disease progression, the indicative scan(s) is/are to be submitted immediately to iCRO for BICR verification of progression. After submission of scan(s), the iCRO will email the assessment to the site and Sponsor.

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

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

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

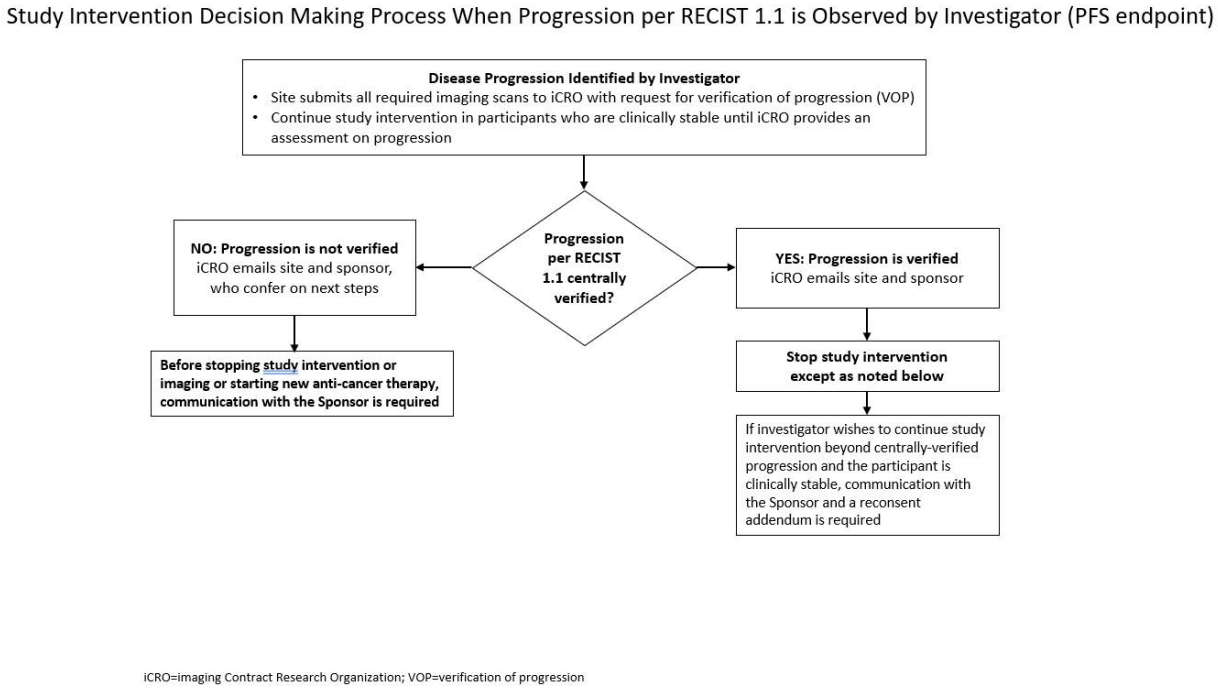
If disease progression is verified, the process continues as follows:

- investigator judgment will determine action
- if the participant is clinically stable and study intervention is to continue, communication with the Sponsor is required and a reconsent addendum must be signed
- obtain scans locally per original protocol schedule
- do not send scans to iCRO

Figure 5 illustrates the study intervention decision process involving verification of disease progression for participants.

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

Figure 5 Study Intervention Decision Making Process When Progression per RECIST 1.1 is Observed by Investigator (PFS endpoint)



iCRO=imaging Contract Research Organization; VOP=verification of progression

8.2.2 Patient-reported Outcomes

As of Amendment 05: ePRO assessments will be discontinued. Original protocol text that is contained in this section has been retained for reference.

It is a best practice and strongly recommended that ePROs are administered before any other visit procedures and in the order listed in the SoA, starting with EuroQoL EQ-5D-5L.

Collection begins at C1 and continues until C35 or treatment discontinuation, whichever occurs first.

The PRO questionnaires will be administered:

- Before dosing at Day1, Cycle 1, and then
- Day 1 of every cycle from Cycle 1 through Cycle 9, then
- Day 1 of every other cycle through Cycle 17 (C11, C13, C15, C17), then
- Every 3 cycles through Cycle 35 (C20, C23, C26, C29, C32, C35).
- Obtain at EOT and Safety FU (if EOT and Safety FU occur before C35).

If the EOT visit happens before the end of the study, PROs will be administered at EOT visit.

PROs will also be administered at the 30-day Safety Follow-up visit. In the event the EOT visit is combined with the 30-day Safety Follow-up visit, only the PRO assessments for the EOT visit will be completed.

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

8.3 Safety Assessments

The total amount of blood/tissue to be drawn/collected over the course of the study (from pre study to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in the laboratory or study procedures manual.

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. Height and weight will also be measured and recorded.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard.

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

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 1.3. After the first dose of study intervention, new clinically significant abnormal findings and changes from Screening physical examination findings will be recorded as AEs.

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

8.3.1.2 Directed Physical Examination

For cycles that do not required a full physical examination as defined in Section 1.3, the investigator or qualified designee will perform a directed physical examination as clinically indicated prior to study intervention administration. New clinically significant abnormal findings should be recorded as AEs.

8.3.2 Vital Signs

The investigator or qualified designee will take vital signs at Screening, before the administration of each dose of trial treatment and during the Safety Follow-up visit, as specified in the SoA (Section 1.3).

Vital signs include temperature, heart rate, respiratory rate, weight, and blood pressure.

Height will be measured at Screening only.

- BP and heart rate will be measured after the participant has been resting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.
- Only 1 BP measurement is needed for participants with systolic BP <140 mm Hg and diastolic BR <90 mm Hg. If the participant's initial BP is elevated (ie, systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), the BP measurement should be repeated at least 5 minutes later. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) shows an elevated BP (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

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

8.3.3 Electrocardiograms

Electrocardiograms 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 Echocardiogram or Multiple Gated Acquisition Scan

A MUGA scan (using technetium-based tracer) or an echocardiogram will be performed to assess LVEF as designated in the SoA (Section 1.3). MUGA or echocardiogram scans should be performed locally in accordance with the institution's standard practice. MUGA scans are the preferred modality; however, whichever modality is used for an individual participant at baseline should be repeated for all subsequent LVEF assessments for that participant. LVEFs as assessed by the institution will be entered onto the CRF. Investigator assessment will be based upon institutional reports.

Refer to Appendix 7 for country-specific requirements.

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 or study procedures 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.

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in the Procedures Manual.

Refer to the SoA (Section 1.3) for the timing of laboratory assessments

8.3.5.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2. Refer to Section 6.6 for required dose modifications for drug-related laboratory AEs.

8.3.5.1.1 Hematology and Clinical Chemistry

Hematology (CBC with differential) and clinical chemistry will be performed within 7 days before the first dose of study intervention. Results from Screening laboratory tests must be reviewed before randomization to confirm eligibility. Labs obtained and reviewed on C1D1 before randomization may also be used as the screening value to determine eligibility.

In subsequent cycles, hematology and clinical chemistry will be performed within 3 days before dosing, and results must be reviewed before administration of study intervention.

For sites not able to test lipase locally, lipase testing will be performed using central laboratory and within 3 days of each subsequent cycle. Participants may be dosed while lipase test results are pending, however the results must be reviewed by the investigator when available.

8.3.5.1.2 Urine Dipstick Testing/Urinalysis

Urine dipstick testing and urinalysis will be performed locally within 7 days before the start of study intervention. Results must be reviewed before randomization to confirm eligibility.

Urinalysis obtained and reviewed on C1D1 before randomization may also be used as the screening value to determine eligibility. If 24-hour urine collection for quantitative

assessment of proteinuria is required, randomization and C1D1 is postponed to after proteinuria result is available.

After Screening, urine dipstick testing will be performed within 3 days before Day 1 of every cycle while participants are taking lenvatinib/placebo. Refer to Section 6.6.2.2 for additional testing and monitoring requirements if proteinuria is detected.

Urinalysis will be performed for all participants according to the SoA. For cycles where urinalysis is required, urinalysis will be performed within 3 days before dosing, and results must be reviewed before administration of study intervention.

8.3.5.1.3 Thyroid Function Testing

The screening blood sample for thyroid function testing will be obtained within 7 days before the first dose of study intervention. Labs obtained and reviewed on C1D1 before randomization may also be used as the screening value to determine eligibility.

Thyroid function testing will be performed within 3 days of each subsequent cycle. Participants may be dosed while thyroid function test results are pending, however the results must be reviewed by the investigator when available.

8.3.5.2 Pregnancy Testing

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 24 hours of the first dose of study intervention. If a urine test is positive or not evaluable, a serum test will be required. Participants must be excluded/discontinued from the study in the event of a positive test result. Repeated pregnancy test (such as monthly testing) may be conducted if required by local regulation.

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine or serum) should be conducted at every protocol treatment cycle , as per SoA.
  - Pregnancy testing (urine or serum) should be conducted for the time required to eliminate systemic exposure after the last dose of each study intervention and should correspond with the time frame for the participant's contraception, as noted in Section 5.1. The length of time required to continue pregnancy testing for each study intervention is:
    - 120 days after the last dose of pembrolizumab
    - 30 days after the last dose of lenvatinib/placebo
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3.6 Performance Assessments

8.3.6.1 Eastern Cooperative Oncology Group Performance Status

The ECOG Performance Status is standardized criteria to measure how cancer impacts level of functioning (performance status) in terms of ability to care for oneself, daily activity, and physical ability (walking, working, etc) with grades 0 to 5.

The investigator or qualified designee will assess ECOG status (see Appendix 9) at screening, before the administration of each dose of study intervention and during the follow-up period 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.

Progression of the cancer under study is not considered an AE as described in Section 8.4.6 and Appendix 3.

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

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

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

Adverse events will not be collected for participants during the prescreening period (for determination of archival tissue status) as long as that participant has not undergone any protocol-specified procedure or intervention. If the participant requires a blood draw, fresh tumor biopsy, etc, the participant is first required to provide consent to the main study, and AEs will be captured according to guidelines for standard AE reporting.

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 randomization through 30 days following cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation/randomization through 90 days following cessation of study intervention or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days following pembrolizumab or 30 days following cessation of lenvatinib/placebo, whichever occurs last, must be reported by the investigator. If the participant initiates new anticancer therapy following discontinuation of study intervention, the time period for reporting pregnancies and exposure during breastfeeding is reduced to 30 days following cessation of study intervention.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered 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 8.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

Table 8 Reporting 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 and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. 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). The investigator will also make every attempt to follow nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities toward 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 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 (spontaneously reported to the investigator or their designee) that occurs in a participant during the study are reportable to the Sponsor.

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

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

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

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

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

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 8.4.

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

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

8.4.7 Events of Clinical Interest

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 Sponsor's product, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.
   Lenvatinib overdose without an associated adverse event is not considered an ECI.

2. Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
   *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

8.5 Treatment of Overdose

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

- Pembrolizumab: ≥5 times the protocol-specified dose.
- Lenvatinib: any dose above the protocol-prescribed dose if associated with an adverse event

There is no specific antidote for an overdose of lenvatinib. Due to its high degree of plasma protein binding, lenvatinib is not expected to be dialyzable. Adverse reactions in patients

receiving single doses of lenvatinib as high as 40 mg were similar to those in clinical studies at the recommended dose for differentiated thyroid cancer, RCC, and HCC.

No specific information is available on the treatment of overdose of pembrolizumab or lenvatinib.

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

Reports of pembrolizumab overdose without any associated clinical symptoms or abnormal laboratory results, should be reported using the terminology "accidental or intentional overdose without adverse effect."

8.6 Pharmacokinetics

Pharmacokinetic parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

As of Amendment 05: Biomarker sample collections are discontinued. Original protocol text that is contained in this section has been retained for reference.

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

- Blood for genetic analysis
- Blood for RNA analysis
- Blood for serum biomarkers
- Blood for plasma biomarkers
- Blood for circulating tumor nucleic acids
- Tumor tissue
- Stool analysis (optional)

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

Refer to Appendix 7 for country-specific requirements.

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes.

8.9 Future Biomedical Research Sample Collection

FBR samples will not be collected in this study.

8.10 Medical Resource Utilization and Health Economics

All-cause hospitalizations and emergency department visits must be reported in the eCRF from the time of treatment 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.

8.11 Visit Requirements

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

8.11.1 Screening

Documented informed consent must be provided before performing any protocol-specific procedure. Results of a test performed before the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

Screening procedures are to be completed within 28 days before the first dose of study intervention.

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

8.11.2 Initial Treatment Phase

Visit requirements for the Initial Treatment Phase are outlined in the SoA (Section 1.3.1). Specific procedure-related details are provided in Section 8.1.

8.11.2.1 Telephone or Contact Visit

A telephone contact or visit will be conducted by the investigator or medically qualified designee (consistent with local requirements) on Cycle 1 Day 8 to assess participants for

development of early toxicity, as outlined in the SoA (Section 1.3.1). An unscheduled visit can occur before C1D15 if necessary for safety.

8.11.3 Second Course Treatment Phase

Participants who meet the criteria outlined in Section 6.7 may be considered for Second Course treatment with pembrolizumab. Visit requirements for the Second Course Treatment Phase are outlined in the SoA (Section 1.3.2). Specific procedure-related details are provided in Section 8.1.

8.11.4 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

The End-of-Treatment visit will take place at the time study intervention is discontinued for any reason.

If the End-of-Treatment visit takes place approximately 30 days from the last dose of study intervention, a separate Safety Follow-up visit is not required. All procedures required at the End-of-Treatment visit and at the Safety Follow-up visit will be performed as a single visit.

8.11.5 Posttreatment Visit

8.11.5.1 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 retreatment with pembrolizumab may have up to 2 safety follow-up visits: 1 after the Initial Treatment or First Course and 1 after the Second Course.

8.11.5.2 Efficacy Follow-up Visits

As of Amendment 05: Efficacy Follow-up Visits will be discontinued except for participants who are candidates for Second Course treatment and participants in China. Imaging scans will no longer be submitted to the iCRO nor read by BICR. Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 6.7 will move from Efficacy Follow-up to Second Course when they experience investigator-assessed disease progression. Original protocol text that is contained in this section has been retained for reference. (Note: participants in China will continue to have BICR tumor response assessments and will continue to submit scans to the iCRO. Participants in China who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 6.7 will move from Efficacy Follow-up to Second Course when they experience centrally-verified disease progression.)

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than centrally-verified radiographic disease progression will move into Efficacy Follow-up and will 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 centrally-verified disease progression, the start of new anticancer therapy, death, or the end of the study, whichever occurs first. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter Survival Follow-up.

Participants who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 6.7 will move from Efficacy Follow-up to Second Course when they experience centrally-verified disease progression. Second Course study procedure requirements are provided in the SoA (Section 1.3.2).

8.11.5.3 Survival Follow-up Contacts

As of Amendment 05: Survival Follow-up Visits will be discontinued except for participants in China. Those participants remaining on study treatment at the time of Amendment 05 should continue to be monitored in the study through the AE reporting period (Section 8.4). Original protocol text that is contained in this section has been retained for reference.

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

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

- For participants who discontinue treatment intervention and who will not enter Efficacy Follow-up, the first survival follow-up contact will be scheduled 12 weeks after the Discontinuation Visit and/or Safety Follow-up Visit (whichever is last).
- For participants who completed assessments in Efficacy Follow-up, the first survival follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

8.11.6 Vital Status

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

9 STATISTICAL ANALYSIS PLAN

As of Amendment 05: The Statistical Analysis Plan is amended as follows.

NOTE: Based on the data from an interim safety and efficacy analysis for LEAP-010 (data cutoff 30-MAY-2023), the study will be discontinued due to lack of efficacy because pembrolizumab in combination with lenvatinib did not demonstrate an improvement in OS, one of the trial's primary endpoints, compared to pembrolizumab plus placebo and appears unlikely to do so in a future analysis. Based upon these data and the recommendation of the eDMC, the study was unblinded on 16-AUG-2023. The prespecified interim analysis 3 (IA3) and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further planned analyses for efficacy and ePRO endpoints.

This section outlines the statistical analysis strategy and procedures for the study. The study has been unblinded as of 16-AUG-2023. Changes made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses that occurred prior to Amendment 05 were documented in previous protocol amendments(s) (consistent with International Conference on Harmonisation [ICH] Guideline E-9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but before the conduct of any analysis, will be documented in an sSAP and referenced in the CSR for the study. The PRO analysis plan will also be included in the sSAP.

Details pertaining to the statistical analyses for participants enrolled in China will be provided in a separate sSAP.

9.1 Statistical Analysis Plan Summary

Key elements of the SAP are summarized below. The comprehensive plan is provided in Section 9.2 – Responsibility for Analyses/In-House Blinding through Section 9.12 – Extent of Exposure. As of Amendment 05, the prespecified IA3 and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further planned analyses of efficacy and ePRO endpoints. The SAP summary has been updated accordingly.

Study Design Overview	A Phase 3 study of pembrolizumab (MK-3475) with or without lenvatinib (E7080/MK-7902) as 1L intervention in a PD-L1 selected population with R/M HNSCC (LEAP-010)
Treatment Assignment	Approximately 500 participants will be randomized in a 1:1 ratio treatment groups: (1) the pembrolizumab + lenvatinib arm and (2) the pembrolizumab + placebo arm. Stratification factors are: • PD-L1 tumor expression as determined by PD-L1 immunohistochemistry (TPS <50% vs. ≥50%) • HPV status for oropharynx cancer as determined by p16 immunohistochemistry (positive vs. negative); HPV status for participants without oropharynx cancer (eg, cancers of the oral cavity, hypopharynx and larynx) is considered HPV negative. • ECOG performance status (0 vs. 1) This is a randomized double-blind study.
Analysis Populations	Efficacy: Intent-to-Treat Safety: All-Participants-as-Treated
Primary Endpoints	ORR, PFS, OS
Statistical Methods for Key Efficacy Analyses	The primary hypotheses addressing PFS and OS will be evaluated by comparing the experimental group to the control group using a stratified log-rank test. The hazard ratio will be estimated using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method. The stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] with strata weighted by sample size will be used for the analysis of the primary hypothesis addressing ORR.
Statistical Methods for Key Safety Analyses	For analyses in which 95% CIs will be provided for between-treatment differences in the percentage of participants with events, these analyses will be performed using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].

Interim Analyses	As of Amendment 05, the prespecified IA3 and final analysis of the study described in the SAP will not be performed. **Efficacy** Three interim analyses are planned in this study. Results will be reviewed by an external DMC. Details are provided in Section 9.7. • Interim Analysis 1 (IA1): - Timing: to be performed after 350 participants are randomized with 6 months of follow-up - Primary purpose: efficacy analysis for ORR and PFS • Interim Analysis 2 (IA2): - Timing: to be performed after both ~432 PFS events have been observed and ~ 6 months after last participant randomized - Primary purpose: efficacy analysis for PFS and OS • Interim Analysis 3 (IA3): - Timing: to be performed after both ~326 OS events have occurred and ~ 14 months after last participant randomized - Primary purpose: efficacy analysis for OS • Final Analysis (FA): - Timing: to be performed after both ~361 OS events have occurred and ~ 20 months after last participant randomized - Primary purpose: efficacy analysis for OS Note that for IA2, IA3 and the FA, if the events accrue more slowly than expected, the analysis can be delayed up to 3 months after the projected timing. **Safety**: The first safety interim analysis will be performed and reviewed by the eDMC at 6 months after the first participant is randomized, or when the first 60 participants have been randomized, whichever is later. Afterwards, the eDMC will review safety data periodically in the study. Details will be included in the DMC charter.
Multiplicity	The overall Type I error over the primary hypotheses is strongly controlled at 2.5% (1-sided), with 0.25% initially allocated to ORR (H1), 0.1% to PFS (H2), and 2.15% to OS (H3). By using the graphical approach of Maurer and Bretz [Maurer, W. and Bretz, F. 2013], if one hypothesis is rejected, the alpha will be shifted to other hypotheses as described in Section 9.8.

Sample Size and Power	As of Amendment 05, the IA3 and final analysis of the study described in the SAP will not be performed. The planned sample size is approximately 500 participants. There will be 350 participants randomized with at least 6 months of follow-up at the ORR final analysis. The study has 90.4% power for detecting a 20-percentage point difference between treatment arms with an underlying 20% response rate in the control arm at an initially assigned 0.0025 (1-sided) significance level. It is estimated that there will be ~ 432 events at the PFS final analysis (ie, IA2 of the study). With 432 PFS events, the study has >99.9% power for detecting a hazard ratio of 0.5 at an initially assigned 0.001 (1-sided) significance level. There will be ~ 361 deaths at the OS final analysis. With 361 deaths, the study has ~90.7% power for detecting a hazard ratio of 0.7 at an initially assigned 0.0215 (1-sided) significance level.

9.2 Responsibility for Analyses/In-house Blinding

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

After efficacy IA2, the study was unblinded on 16-AUG-2023.

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

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

The investigator and the study team at the Sponsor consisting of clinical, statistical, statistical programming and data management personnel will be blinded to participant-level PD-L1 biomarker score. An unblinded Sponsor statistician and unblinded Sponsor statistical programmer will have access to the participant-level PD-L1 results for the purpose of data review and will have no other responsibilities associated with the study. A summary of PD L1 biomarker prevalence may be provided to the study team at the Sponsor by the unblinded Sponsor statistician. In addition, the independent radiologist(s) will perform the central imaging review without knowledge of treatment group assignment.

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

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0 – Hypotheses, Objectives and Endpoints.

9.4 Analysis Endpoints

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

9.4.1 Efficacy Endpoints

Primary

- **Objective Response Rate**

The ORR is defined as the percentage of participants who achieve a confirmed complete response or partial response per RECIST 1.1 as assessed by BICR.

- **Progression-free Survival**

PFS is defined as the time from randomization to the first documented disease progression per RECIST 1.1 by BICR or death due to any cause, whichever occurs first. See Section 9.6.1 – Statistical Methods for Efficacy Analyses for definition of censoring.

- **Overall Survival**

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

Secondary

- **Duration of Response**

For participants who show confirmed CR or PR, duration of response is defined as the time from the first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.

9.4.2 Safety Endpoints

Safety measurements are described in Section 4.2.1.2 – Safety Endpoints and Section 8 – Study Assessments and Procedures. Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests and vital signs. Safety parameters to be analyzed include, but are not limited to, AEs, SAEs, fatal AEs, and laboratory changes.

9.4.3 Patient-Reported Outcome Endpoints

Changes from baseline in the global health status/quality of life and physical functioning scores of the EORTC QLQ-C30 will be evaluated as overall measures of HRQoL. Additional details of the PRO endpoints, including analyses of the remaining functioning and symptom scores of the EORTC QLQ-C30 and EORTC QLQ-H&N35 and health status scores of the EQ-5D-5L, will be described in the sSAP.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The ITT population will serve as the population for the primary efficacy analyses. For the analyses of ORR, approximately the first 350 or more randomized participants will be included in the analysis population. For the analyses of PFS and OS, all randomized participants will be included in the ITT population. For the analyses of DOR, the subset of participants who show a confirmed complete response or partial response will be included in the analysis population. Participants will be included in the treatment group to which they are randomized.

9.5.2 Safety Analysis Populations

Safety analyses will be conducted in the APaT population, which consists of all randomized participants who received at least one dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who take incorrect study treatment for the entire treatment period; such participants will be included in the treatment group corresponding to the study treatment actually received.

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

9.5.3 Patient-Reported Outcome Analysis Populations

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

9.5.4 Population Pharmacokinetic Analysis Set

No pharmacokinetic endpoints are planned for this study.

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

NOTE: As of Amendment 05, the prespecified IA3 and final analysis of the study described in the SAP will not be performed. Safety analysis will be performed at the end of the study; there will be no further planned analyses of efficacy and ePRO endpoints. Original protocol text that is contained in this section has been retained for reference.

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

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, Multiplicity. Nominal p-values may be computed for other efficacy analyses but should be interpreted with caution due to potential issues of multiplicity and sample size.

The stratification factors used for randomization (see Section 6.3.2 - Stratification) will be applied to all stratified analyses, in particular, the stratified log-rank test, stratified Cox model, and stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. If there are small strata, for the purpose of analysis, strata will be combined to ensure sufficient number of participants, responses or events in each stratum. Details regarding the pooling strategy will be prespecified in the sSAP before the database lock for the first efficacy interim analysis, and decisions regarding the pooling will be based on a blinded review of response and event counts by stratum.

9.6.1.1 Objective Response Rate

The stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985] will be used for comparison of the ORR between two treatment groups. The difference in ORR and its 95% confidence interval from the stratified Miettinen and Nurminen method with strata weighting by sample size will be reported. The stratification factors used for randomization (See Section 6.3.2 - Stratification) will be applied to the analysis. The point estimate of ORR will be provided by treatment group, together with 95% CI using exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934]. Supportive analyses may be performed for comparison of ORR based on investigator's assessment.

9.6.1.2 Progression-free Survival

The nonparametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, hazard ratio) between the treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (See Section 6.3.2 - Stratification)

will be applied to both the stratified log-rank test and the stratified Cox model. Supportive analyses may be performed for comparison of PFS based on investigator's assessment.

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. The true date of disease progression will be approximated by the earlier of the date of the first assessment at which PD is objectively documented per RECIST 1.1 by BICR and the date of death. Death is considered a PD event.

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

To evaluate the robustness of the PFS endpoint per RECIST 1.1 by BICR, 2 sensitivity analyses with different sets of censoring rules will be performed. The first sensitivity analysis follows the intention-to-treat principle. That is, PDs/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 complete response 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 the primary and sensitivity analyses are summarized in Table 9.

Table 9 Censoring Rules for Primary and Sensitivity Analyses of PFS

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 assessment and new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study treatment or completed study treatment.
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment

Abbreviations: PD = disease progression; PFS = progression-free survival.

9.6.1.3 Overall Survival

The nonparametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test. 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 hazard ratio). The hazard ratio and its 95% confidence interval from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (See Section 6.3.2 - Stratification) 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 the participant was last known to be alive.

9.6.1.4 Duration of Response

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

Censoring rules for DOR are summarized in Table 10.

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

Table 10 Censoring Rules for DOR

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 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)

Abbreviations: DOR = duration of response; PD = disease progression.
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 Variables

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

Table 11 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses			
ORR per RECIST 1.1 by BICR	Testing and estimation: stratified Miettinen and Nurminen method	ITT	Participants with missing data are considered nonresponders
PFS per 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 9
OS	Testing: stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at participant's last known alive date

Abbreviations: BICR = blinded independent central review; ITT = intent-to-treat; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors.

The strategy to address multiplicity issues with regard to multiple endpoints and interim analyses is described in Section 9.7 (Interim Analyses) and Section 9.8 (Multiplicity).

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 and vital signs.

The analysis of safety results will follow a tiered approach (Table 12). The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as system organ class terms) and events that meet predefined limits of change in laboratory and vital signs parameters are either prespecified as "Tier 1" endpoints or will be classified as belonging to "Tier 2" or "Tier 3" based on the observed proportions of participants with an event.

Tier 1 Events

Safety parameters or adverse events of special interest that are identified a priori constitute "Tier 1" safety endpoints that will be participant to inferential testing for statistical significance. AEs 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. Finally, there are no known AEs associated with participants with HNSCC for which determination of a p-value is expected to impact the safety assessment. Thus, there are no AEs that warrant elevation to Tier 1 in this study.

Tier 2 Events

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

Membership in Tier 2 requires that at least 10% of participants in any treatment group show the event; all other AEs will belong to Tier 3. The threshold of at least 10% of participants was chosen for Tier 2 events because the population enrolled in this study is in critical condition and usually experiences various AEs of similar types regardless of treatment; events reported less frequently than 10% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, Grade 3 to 5 AEs (≥5% of participants in 1 of the treatment groups), SAEs (5% of participants in 1 of the treatment groups) and tumor hemorrhage (incidence ≥4 of participants in one of the treatment groups) will be considered Tier 2 endpoints. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not as a formal method for assessing the statistical significance of the between-group differences.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. The broad AE categories consisting of the proportion of participants with any AE, any drug-related AE, any Grade 3 to 5 AE, any serious AE, any AE which is both drug-related and Grade 3 to 5, any AE which is both serious and drug-related, discontinued due to an AE, and death that are not prespecified as Tier 1 endpoints will be classified as belong to "Tier 3". Laboratory test toxicity grade shift from baseline will be considered Tier 3 event. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Continuous Safety Measures

Continuous measures such as changes from baseline in vital signs parameters will be considered Tier 3 event. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group for vital signs parameters.

Table 12 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Specific Grade 3-5 AE (incidence ≥5% of participants in one of the treatment groups)		X	X
	Specific serious AE (incidence ≥5% of participants in one of the treatment groups)		X	X
	Specific AEs, SOCs (incidence ≥10% of participants in one of the treatment groups)		X	X
	Tumor hemorrhage (incidence ≥ 4 of participants in one of the treatment groups)		X	X
Tier 3	Any AE			X
	Any Grade 3-5 AE			X
	Any Serious AE			X
	Any Drug-Related AE			X
	Any Serious and Drug-Related AE			X
	Any Grade 3-5 and Drug-Related AE			X
	Discontinuation due to AE			X
	Death			X
	Specific AEs, SOCs (incidence > 0% of participants in all of the treatment groups)			X
	Change from Baseline Results (lab toxicity shift, vital signs)			X
Abbreviations: AE = adverse event; CI = confidence interval; SOC = system organ class.				

9.6.3 Statistical Methods for Patient-Reported Outcome Analyses

Details of PRO analyses will be described in the sSAP.

9.6.4 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

NOTE: As of Amendment 05, the prespecified IA3 and final analysis of the study described in the SAP will not be performed. This section is retained for reference.

Access to the allocation schedule for summaries or analyses for presentation to the eDMC will be restricted to an unblinded statistician and an unblinded scientific programmer performing the interim analysis, who will have no other responsibilities associated with the study.

The eDMC will serve as the primary reviewer of the results of the interim analyses and will make recommendations for discontinuation of the study or modification to the executive oversight committee of the Sponsor. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive oversight committee and potentially other limited Sponsor personnel may be unblinded to results at the treatment level to act on these recommendations. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the unblinded team. Additional logistic details will be provided in the eDMC Charter.

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

9.7.1 Efficacy Interim Analyses

Three interim analyses are planned in addition to the final analysis for this study. Interim Analysis 1 will include at least 350 participants with 6 months of follow-up, and the other interim analyses and final analysis will include all randomized participants. Results of the interim analyses will be reviewed by the DMC. Details of the boundaries for establishing statistical significance with regards to efficacy are discussed further in Section 9.8.

The analyses planned, endpoints evaluated, and drivers of timing are summarized in Table 13.

Table 13 Summary of Interim and Final Analyses Strategy

Analyses	Key Endpoints	Timing[a]	Estimated Time after First Participant Randomized	Primary Purpose of Analysis
IA1	ORR PFS	At least 350 participants randomized with ~ 6 months of follow-up	~ 24 months	• Final ORR analysis • Interim PFS analysis
IA2	PFS OS	Both ~ 432 PFS events have occurred and ~ 6 months after last participant randomized	~ 30 months	• Final PFS analysis • Interim OS analysis
IA3	OS	Both ~ 326 deaths have occurred and ~ 14 months after last participant randomized	~ 38 months	• Interim OS analysis
FA	OS	Both ~ 361 deaths have occurred and ~ 20 months after last participant randomized	~ 44 months	• Final OS analysis

Abbreviations: FA = final analysis; IA1 = interim analysis 1; IA2 = interim analysis 2; IA3 = interim analysis 3; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

a For IA2, IA3 and FA, if the events accrue slower than expected, the analysis can be delayed up to 3 months after the projected timing, ie, the Sponsor may conduct IA2, IA3 and FA when all participants have been followed up for 9, 17 months and 23 months, respectively.

9.7.2 Safety Interim Analysis

The eDMC was responsible for periodic interim safety reviews as specified in the DMC charter. Details were included in the DMC charter. Safety monitoring will continue as per protocol.

9.8 Multiplicity

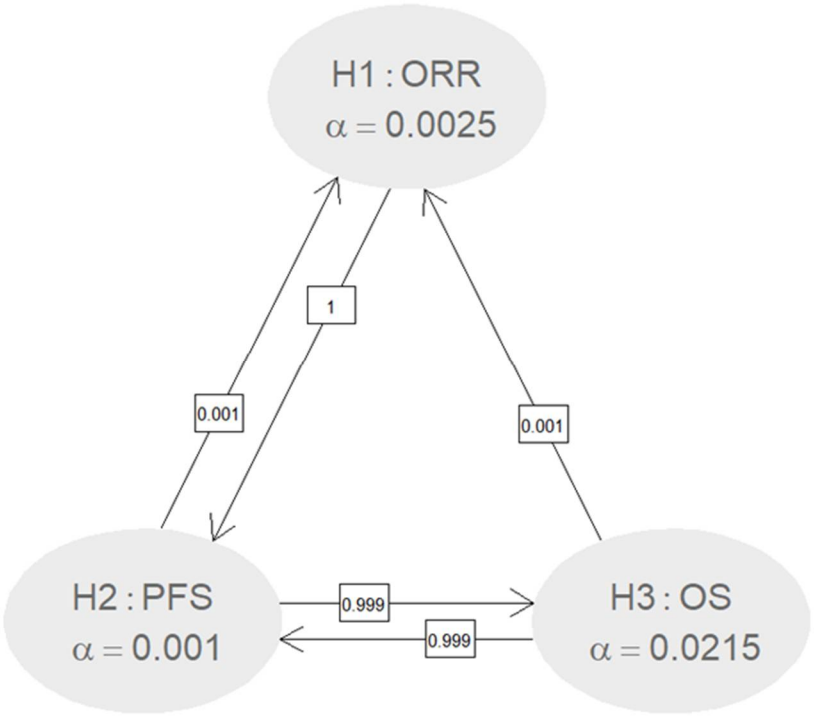
NOTE: As of Amendment 05, the prespecified IA3 and final analysis of the study described in the SAP will not be performed. Original protocol text that is contained in this section has been retained for reference.

The study uses the graphical method of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] to control multiplicity for multiple hypotheses as well as interim analyses. 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 6 shows the initial 1-sided α allocation for each hypothesis in the ellipse representing the hypothesis. The weights for re-allocation from each hypothesis to the others are shown in the boxes on the lines connecting hypotheses.

The overall Type-I error is strongly controlled at 0.025 (1-sided) for the 3 primary endpoints ORR, PFS and OS. The initial α assigned to ORR, PFS, and OS will be 0.0025, 0.001 and 0.0215, respectively. If the PFS hypothesis is rejected, the corresponding alpha can be reallocated to OS. If the OS hypothesis is rejected, the corresponding alpha can be reallocated to PFS. If ORR hypothesis is rejected, the corresponding alpha can be reallocated

to PFS. If both the OS and PFS hypotheses are rejected, the corresponding alpha can be reallocated to ORR.

Figure 6 Multiplicity Diagram for Type I Error Control



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

9.8.1 Objective Response Rate

The study will test ORR only once at IA1, at an initial α level of 0.0025 (Figure 6). Note that if superiority for both the PFS and OS hypotheses is declared at a future planned analysis, α=0.0225 will be rolled over to the hypothesis for ORR, then the test statistics previously computed at IA1 for the ORR hypothesis will be used for inferential testing with an updated alpha level of 0.025.

Based on the first 350 randomized participants with at least 6 months of follow-up, power at the possible α-levels as well as the approximate treatment difference required to reach the bound (ΔORR) are shown in Table 14, assuming underlying 20% and 40% response rates in the control and experimental groups, respectively.

Table 14 Possible α Levels (One-Sided) and Approximate ORR Difference Required to Show Efficacy for Objective Response at IA1

α (One-Sided)	~Δ ORR	Power
0.0025	0.1327	0.904
0.025	0.0901	0.985
Abbreviation: ORR = objective response rate.		

9.8.2 Progression-free Survival

The study will test PFS at IA1 and IA2 only. After the multiplicity strategy as outline in Figure 6, the PFS hypothesis may be tested at α=0.001 (initially allocated α), at α=0.0035 (if the ORR null hypothesis is rejected but not the OS hypothesis), at α=0.0225 (if the OS null hypothesis is rejected but not the ORR hypothesis), or at α=0.025 (if both the OS and ORR null hypotheses are rejected). For the superiority hypothesis, a Lan-DeMets O'Brien-Fleming alpha spending function is used to construct group sequential boundaries to control the Type-I error rate. Table 15 shows the boundary properties for each of these α levels for the PFS analysis. Note that the final row indicates the total power to reject the null hypothesis for PFS at each α level. Also, note that if the OS null hypothesis is rejected at IA3 or FA of the study, the previously computed PFS test statistics may be used for inferential testing with its updated bounds, considering the α reallocation from the OS hypothesis.

For the PFS hypothesis H2, IA2 will be the final PFS analysis with a target number of events of 432. The bounds provided in Table 15 are based on the assumption that the number of events at IA1 and IA2 are 350 and 432, respectively. At the time of an analysis, the observed number of events may differ substantially from the expected. To avoid overspending at IA1 and keep reasonable alpha for the IA2, the minimum alpha spending strategy will be adopted. At IA1, the information fraction used in Lan-DeMets spending function to determine the alpha spending at the IA will be based on the minimum of the expected information fraction and the actual information fraction at the analysis.

- In the scenario that the event accumulation is faster than expected, ie, if the number of observed events exceeds the expected number of events at IA1, then the information fraction will be calculated as the expected number of events at IA1 over the target number of events at IA2.
- In the scenario that the event accumulation is slower than expected and number of events is less than the expected number of events in the table when IA1 is conducted, the information fraction will be calculated as the actual number of events at IA1 over the target number of events at IA2.

The final PFS analysis will use the remaining Type I error that was not spent at the earlier analysis. The p-value bound at the final PFS analysis will be calculated by considering the correlation between the test statistics as determined by the actual number of PFS events at IA1 and IA2 of the study.

Table 15 Efficacy Boundaries and Properties for Progression-free Survival Analyses

Analysis	Value	α=0.001	α=0.0035	α=0.0225	α=0.025
IA1: 81%* N = 500 Events: 350 Month: 24	Z	3.4757	3.0428	2.2833	2.2344
	p (1-sided) [a]	0.0003	0.0012	0.0112	0.0127
	HR at bound[b]	0.6893	0.7221	0.7832	0.7873
	P(Cross) if HR=1[c]	0.0003	0.0012	0.0112	0.0127
	P(Cross) if HR=0.5[d]	0.9988	0.9997	1.0000	1.0000
IA2 N = 500 Events: 432 Month: 30	Z	3.1149	2.7327	2.0698	2.0276
	p (1-sided) [a]	0.0009	0.0031	0.0192	0.0213
	HR at bound[b]	0.7408	0.7686	0.8193	0.8226
	P(Cross) if HR=1[c]	0.0010	0.0035	0.0225	0.0250
	P(Cross) if HR=0.5[d]	1.0000	1.0000	1.0000	1.0000

Abbreviations: HR = hazard ratio; IA = interim analysis.
The number of events and timings are estimated approximately.
*Percentage of the target number of events at final analysis anticipated at interim analysis
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=0.5) is the probability of crossing a bound under the alternative hypothesis.

9.8.3 Overall Survival

The study will test OS at IA2, IA3 and FA. After the multiplicity strategy as outlined in Figure 6 the OS hypothesis may be tested at α=0.0215 (initially allocated α), or α=0.0225 (if the PFS null hypothesis is rejected but not the ORR hypothesis), or α=0.025 (if both the PFS and ORR null hypotheses are rejected). For the superiority hypothesis, a Lan-DeMets O'Brien-Fleming alpha spending function is used to construct group sequential boundaries to control the Type I error rate. Table 16 shows the boundary properties for each of these α levels for the OS analysis. The bounds provided in the table are based on the assumption that the number of events at IA2, IA3 and FA are 258, 326 and 361, respectively. At the time of an analysis, the observed number of events may differ substantially from the expected. To avoid overspending at an interim analysis and keep reasonable alpha for the final analysis, the minimum alpha spending strategy will be adopted. At an IA, the information fraction used in Lan-DeMets spending function to determine the alpha spending at the IA will be based on the minimum of the expected information fraction and the actual information fraction at each analysis.

- In the scenario that the event accumulation is faster than expected, ie, if the number of observed events exceeds the expected number of events at an interim analysis, then the information fraction will be calculated as the expected number of events at the interim analysis over the target number of events at FA.
- In the scenario that the event accumulation is slower than expected and number of events is less than the expected number of events in the table when an interim analysis is conducted, the information fraction will be calculated as the actual number of events at the interim analysis over the target number of events at FA.

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

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

Table 16 Efficacy Boundaries and Properties for Overall Survival Analyses

Analysis	Value	α=0.0215	α =0.0225	α =0.025
IA2: 71%* N = 500 Events: 258 Month: 30	Z	2.4857	2.4636	2.4120
	p (1-sided)[a]	0.0065	0.0069	0.0079
	HR at bound[b]	0.7334	0.7355	0.7403
	P(Cross) if HR=1[c]	0.0065	0.0069	0.0079
	P(Cross) if HR=0.7[d]	0.6476	0.6557	0.6747
IA3: 90%* N: 500 Events: 326 Month: 38	Z	2.2091	2.1901	2.1457
	p (1-sided)[a]	0.0136	0.0143	0.0159
	HR at bound[b]	0.7828	0.7845	0.7884
	P(Cross) if HR=1[c]	0.0155	0.0163	0.0183
	P(Cross) if HR=0.7[d]	0.8509	0.8553	0.8655
FA N: 500 Events: 361 Month: 44	Z	2.1297	2.1119	2.0702
	p (1-sided)[a]	0.0166	0.0173	0.0192
	HR at bound[b]	0.7991	0.8006	0.8042
	P(Cross) if HR=1[c]	0.0215	0.0225	0.0250
	P(Cross) if HR=0.7[d]	0.9070	0.9100	0.9169

Abbreviations: FA = final analysis; HR = hazard ratio; IA = interim analysis.
The number of events and timings are estimated approximately.
*Percentage of the target number of events at final analysis anticipated at interim analysis.
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=0.7) is the probability of crossing a bound under the alternative hypothesis.

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

9.8.4 Safety Analyses

The DMC has responsibility for assessment of overall risk/benefit. When prompted by safety concerns, the DMC can request corresponding efficacy data. DMC review of efficacy data to

assess the overall risk/benefit to study participants will not require a multiplicity adjustment typically associated with a planned efficacy interim analysis. However, to account for any multiplicity concerns raised by the DMC 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

NOTE: As of Amendment 05, the prespecified IA3 and final analysis of the study described in the SAP will not be performed. This section is retained for reference.

The study will randomize 500 participants in a 1:1 ratio into the pembrolizumab + lenvatinib arm and pembrolizumab + placebo arm. ORR, PFS and OS are primary endpoints for the study.

Based on the 350 participants with at least 6 months of follow-up, the power of the ORR testing at the initially allocated α=0.0025 (1-sided) is approximately 90.4% to detect a 20-percentage point difference between an underlying 20% response rate in the control arm and a 40% response rate in the experimental arm.

For the PFS endpoint, based on a target number of 432 events at the final analysis and 1 interim analysis at approximately 81% of the target number of events, the study has approximately >99.9% power to detect a hazard ratio of 0.5 at the initially allocated α=0.001 (1-sided).

For the OS endpoint, based on a target number of 361 events and 2 interim analyses at approximately 71% and 90% of the target number of events, the study has approximately 90.7% power to detect a hazard ratio of 0.7 at the initially allocated α=0.0215 (1-sided).

Based on [Burtness, B., et al 2018], the above sample size and power calculations for PFS and OS assume the following:

- PFS follows an exponential distribution with a median of 3 months for the control group.
- OS follows an exponential distribution with a median of 12 months for the control group.
- Enrollment period of 24 months with enrollment ramp-up over first 6 months.
- An annual dropout rate of 5% for PFS and OS.
- A follow-up period of 6 and 20 months for PFS and OS, respectively, after the last participant is randomized.

The sample size and power calculations were performed using R (“gsDesign” package) and SAS 9.4.

9.10 Subgroup Analyses

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

- Stratification factors
  - PD-L1 tumor expression as determined by PD-L1 immunohistochemistry (TPS <50% vs. ≥50%)
  - HPV status for oropharynx cancer as determined by p16 immunohistochemistry (positive vs. negative); HPV status for participants without oropharynx cancer (eg, cancers of the oral cavity, hypopharynx and larynx) is considered HPV negative.
  - ECOG performance status (0 vs. 1)
- Age category (<65 years, ≥65 years)
- Sex (female, male)
- Race (white, all others)
- Geographic region (North America, European Union, Asia, Rest of the World)
- PD-L1 tumor expression as determined by PD-L1 immunohistochemistry (CPS <50 vs. ≥50)

A forest plot will be produced, which provides the estimated point estimates and confidence intervals for the treatment effect across the categories of subgroups listed above. If the number of participants in a category of a subgroup variable is less than 10% of the ITT population, the subgroup analysis will not be performed for this category of the subgroup variable, and this subgroup variable will not be displayed in the forest plot. The subgroup analyses for PFS and OS will be conducted using an unstratified Cox model, and the subgroup analyses for ORR will be conducted using the unstratified Miettinen and Nurminen method.

9.11 Compliance (Medication Adherence)

Drug accountability data for trial 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 and number of days in which the participant receives the study intervention. Summary statistics will be provided on the extent of exposure for the overall study intervention, and for pembrolizumab and lenvatinib separately 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 and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. 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 (or individuals acting on behalf of MSD) 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 Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct or serious GCP-non-compliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

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

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

III. Participant Protection

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

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

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate

an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

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

The following committees will have responsibilities regarding this protocol:

10.1.4.1 Scientific Advisory Committee (SAC)

This study was developed in collaboration with an SAC. The SAC is comprised of both Sponsor and non-Sponsor scientific experts who provide input with respect to study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

10.1.4.2 Executive Oversight Committee

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

10.1.4.3 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other

way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

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

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

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

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

Authorship will be determined by mutual agreement and in line with 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, ICH 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 Trials.

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection,

copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

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

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

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

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 17 will be performed by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 17 Protocol-required Clinical Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	WBC count with differential[a]: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	RBC Indices: MCV[b] MCH[b] %Reticulocytes[b]	
Chemistry	Albumin	Blood Urea Nitrogen (BUN) [c]	Creatinine [d]	Potassium
	Glucose	Calcium	Sodium	Magnesium
	Amylase	Lipase		
	Total bilirubin (and direct bilirubin if total bilirubin is elevated above the upper limit of normal)	Aspartate Aminotransferase (AST)/ Serum Glutamic Oxaloacetic Transaminase (SGOT)	Alanine Aminotransferase (ALT)/ Serum Glutamic Pyruvic Transaminase (SGPT)	Alkaline phosphatase
	Total Protein[b]	Bicarbonate[b]	Chloride[b]	Phosphorous[b]
Thyroid Function Tests	Thyroid-stimulating hormone (TSH)	Triiodothyronine (total T3)[e]	Free thyroxine (FT4)	
Coagulation [f]	International normalized ratio (INR) or prothrombin time (PT)		Activated partial thromboplastin time (aPTT) [g]	
Routine Urinalysis	Specific gravity pH, glucose, protein[h], blood, ketones, by dipstick Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	Follicle-stimulating hormone (as needed in women of nonchildbearing potential only) Serum or urine β human chorionic gonadotropin (β hCG) pregnancy test (as needed for WOCBP) Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) (if required by local health authority)			

Laboratory Assessments	Parameters
NOTES: a Absolute Neutrophil Count (ANC) is required at Screening to confirm eligibility. After Screening, absolute or % acceptable per institutional standard. b Performed only if considered local standard of care. c Urea is acceptable if BUN is not available as per institutional standard. d GFR (measured or calculated) or creatinine clearance can be used in place of creatinine. e Free T3 is acceptable where total T3 cannot be determined. f Refer to Section 6.6.2.2 for additional testing/monitoring required for proteinuria. g PTT may be performed if the local laboratory is unable to perform aPTT h Performed as part of the screening assessment and as clinically indicated for participants taking anticoagulants	

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, medical device, combination product, 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 preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of 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 in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

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

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

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

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 5. 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 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.

  Note: A semi-colon indicates 'or' within the description of the grade.

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

- 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: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

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

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

Women in the following categories are not considered WOCBP:

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

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

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[b] • IUS[c] • Nonhormonal 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 for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [c] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: • Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. • Male condom with cap, diaphragm, or sponge with spermicide. • Male and female condom should not be used together (due to risk of failure with friction).

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

Not applicable

10.7 Appendix 7: Country-specific Requirements

10.7.1 Canada

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

Section 6.6.2.9 Management of Gastrointestinal Perforation or Fistula Formation

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

10.7.2 China

Section 1.1 Synopsis and Section 1.2 Schema

Participants in China will continue participation this trial until all regulatory commitments have been met. Upon completion of all regulatory requirements, participants in China are to be discontinued and may be enrolled in an extension study using pembrolizumab in combination with compound (eg, lenvatinib) if available.

Section 4.1 Overall Design

After enrollment of the global portion of the study is complete, the study may remain open to enrollment in China alone until the target number of participants in China has been enrolled to meet local regulatory requirements.

Section 8.8 Biomarkers

Biomarker sample collection for participants enrolled in China will be dependent on approval by the Human Genetic Resources Administration of China

10.7.3 Germany

In Germany, the assessment that is in line with the standard of care is the ECHO scan. Therefore, in Germany, the participating sites will perform an ECHO scan as required per protocol. In the clinical study, the MUGA scan is not allowed in Germany as no German Federal Office for Radiation Protection BfS (Bundesamt für Strahlenschutz) approval has been obtained for this assessment.

10.7.4 Japan

Section 6.1 Study Intervention(s) Administered

Table 4 – Study Interventions

Pembrolizumab IV used in this study is categorized as “product(s) used in the clinical trial other than test product(s)” in Japan local regulation.

10.7.5 UK

Section 6.5 Concomitant Therapy

Listed below are specific concomitant therapies or vaccinations that are prohibited during the study (exceptions noted):

- Live vaccines must not be administered for 90 days after the last dose of study intervention. Refer to Section 6.5 for information on COVID-19 vaccines.

  Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country 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.

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

Not applicable.

10.9 Appendix 9: ECOG Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	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	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655

http://ecog-acrin.org/resources/ecog-performance-status

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
ACCP	American College of Chest Physicians
ADA	antidrug antibodies
ADL	activities of daily living
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
AR	adverse reaction
ART	antiretroviral therapy
AST	aspartate aminotransferase
ATD	accelerated titration design
ATP	adenosine triphosphate
AUC	area under the curve
BCG	Bacillus Calmette–Guérin
BDS	blood drug screen
BICR	blinded independent central review
bid	twice daily
BMI	body mass index
BP	blood pressure
CAC	Clinical Adjudication Committee
CCU	Cardiac care unit
CD28	cluster of differentiation 28
CD3ζ	CD3 zeta
CF	compact flash
CG	Cockcroft-Gault
CHS	cough hypersensitivity syndrome
CI	confidence interval
C_{max}	maximum plasma concentration

Abbreviation	Expanded Term
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
CPS	combined positive score
CrCl	creatinine clearance
CR	complete response
CRF	Case Report Form
CRU	clinical research unit
CSD	Cough Severity Diary
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE 5.0	Common Terminology Criteria for Adverse Events, Version 5.0
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CTMS	Clinical Trial Management System
CYP	cytochrome P450
DAIDS	Division of AIDS
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
eCTA	exploratory Clinical Trial Application

Abbreviation	Expanded Term
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data collection
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
ePROs	electronic patient-reported outcomes
E-R	exposure response
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FEV1	forced expiratory volume in 1 second
FAS	Full Analysis Set
FFPE	formalin-fixed, paraffin embedded
FIH	first in human
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
HbA1c	hemoglobin A1c
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRQoL	health-related quality of life

Abbreviation	Expanded Term
HRT	hormone replacement therapy
HSSB	Hepatic-specific Safety Board
IA(s)	interim analysis(ses)
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
iCRO	imaging CRO
ICU	intensive care unit
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG4	immunoglobulin G4
IgV	immunoglobulin-variable
IHC	immunohistochemistry
IND	Investigational New Drug
IO	Immune oncology
irAEs	immune-related AEs
IRB	Institutional Review Board
iRECIST	Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
IRT	interactive response technology
ITP	idiopathic thrombocytopenic purpura
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic
IVRS	interactive voice response system
IWG	International Working Group
IWRS	integrated web response system
JRCT	Japan Registry of Clinical Trials

Abbreviation	Expanded Term
KPS	Karnofsky performance status
LAM	lactational amenorrhea method
LCQ	Leicester Cough Questionnaire
LLN	lower limit of normal
LLOQ	lower limit of quantitation
mAb	monoclonal antibody
MAD	maximum administered dose
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MTD	maximum tolerated dose
mTPI	modified Toxicity Probability Interval
NCI	National Cancer Institute
NCS	not clinically significant
NEAB	noneosinophilic bronchitis
NDA	New Drug Application
NOAEL	no observed adverse effect level
OR	objective response
ORR	objective response rate
OS	overall survival
OSF	on-site formulation
OTC	over the counter
PBPK	physiologically based PK
PCL	Protocol Clarification Letter
PD-1	programmed cell death 1 protein
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography

Abbreviation	Expanded Term
PFS	progression free survival
PGIC	Patient Global Impression Change
PK	pharmacokinetic
PKCθ	protein kinase C-theta
po	orally
PP	per-protocol
PQC	product quality complaint
PR	partial response
PRO	patient-reported outcome
Q2W	every 2 weeks
Q3W	every 3 weeks
QoL	quality of life
QP2	Department of Quantitative Pharmacology and Pharmacometrics
RCC	refractory chronic cough
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid
rP2D	recommended Phase 2 dose
RR	respiratory rate
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transminase
SIM	Site Imaging Manual
SLAB	Supplemental laboratory test(s)
SoA	schedule of activities
SOC	standard of care
SOP	Standard Operating Procedures
sSAP	supplemental Statistical Analysis Plan

Abbreviation	Expanded Term
STING	stimulator of interferon genes
SUSAR	suspected unexpected serious adverse reaction
SVR12	sustained viral response
TEA	Treatment Eligibility Assessment (form)
T_{max}	time to maximum plasma concentration
TMDD	target-mediated drug disposition
$t_{½}$	half life
UACS	upper airway cough syndrome
UCC	unexplained chronic cough
UDS	urine drug screen
ULN	upper limit of normal
URTI	upper respiratory tract infection
UTN	Universal Trial Number
Vd	volume of distribution
VAS	Visual Analog Scale
VS	vital signs
WBC	white blood cell
WPAI	Work Productivity and Activity Impairment
ZAP70	zeta-chain-associated protein kinase

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