Official Protocol Title:	A Phase 2, randomized, open-label three-arm clinical study to evaluate the safety and efficacy of lenvatinib (E7080/MK-7902) in combination with pembrolizumab (MK-3475) versus standard of care chemotherapy and lenvatinib monotherapy in participants with recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) that have progressed after platinum therapy and immunotherapy (PD-1/PD-L1 inhibitors) (LEAP-009)
NCT number:	NCT04428151
Document Date:	25-NOV-2024

TITLE PAGE

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Protocol Title: A Phase 2, randomized, open-label three-arm clinical study to evaluate the safety and efficacy of lenvatinib (E7080/MK-7902) in combination with pembrolizumab (MK-3475) versus standard of care chemotherapy and lenvatinib monotherapy in participants with recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) that have progressed after platinum therapy and immunotherapy (PD-1/PD-L1 inhibitors) (LEAP-009)

Protocol Number: 009-07 (E7080-G000-228)

Compound Number: MK-7902

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

The study is co-funded by MSD and Eisai.

Legal Registered Address:

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Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

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EU CT	2022-500820-31
EudraCT	2019-000569-19
JAPIC-CT	Not Applicable
WHO	Not Applicable
UTN	Not Applicable
IND	142277

Approval Date: 25 November 2024

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 7 (Global)	25-NOV-2024	This amendment addresses a change in strategy to stop the study based on the results of a periodic review of safety data using a data cutoff date of 31-MAY-2024 that was conducted by the eDMC. At the request of the eDMC, OS data were provided for review, though there was no preplanned statistical analysis for OS. At this safety analysis, the OS Kaplan-Meier curves did not favor pembrolizumab + lenvatinib versus SOC chemotherapy.
Amendment 6 (Global)	08-JUL-2024	This change was made to address sponsor's strategy to revise the primary endpoint from OR to OS, based on emerging external data for this patient population.
Amendment 5 (Global)	08-SEP-2022	To no longer require the most recent treatment prior to study entry to be anti-PD-1/PD-L1 treatment.
Amendment 4 (Global)	30-MAR-2021	To update the dose modification table for pembrolizumab. To incorporate lenvatinib program level updates. To specify for participants of the UK, Romania, and Portugal that length of contraception for male participants receiving paclitaxel should be at least 6 months from the last dose to be consistent with the paclitaxel SmPC. To provide guidance regarding osteonecrosis of the jaw for participants treated with lenvatinib.
Amendment 03 (UK-specific)	05-NOV-2020	To add updates from Global Protocol Amendment 1.
Amendment 02 (UK-specific)	05-AUG-2020	To address regulatory authority requests, added precautionary measures for participants in the UK to be in accordance with the Summary of Product Characteristics of cetuximab, paclitaxel, docetaxel, and capecitabine. Also, for participants in the UK, required live vaccines to not be administered until 120 days after the last dose of pembrolizumab. Note: This amendment is based on the original protocol per regulatory request.

Document	Date of Issue	Overall Rationale
Amendment 1 (Global)	24-JUL-2020	To clarify that medications known to prolong QT interval must be used cautiously; to clarify that independent retrospective analysis of radiographic response to pre-study treatment with anti-PD-1/PD-L1 therapy may occur; and to provide program-level updates, corrections, and clarifications.
Original Protocol	16-MAR-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 07

Overall Rationale for the Amendment:

This amendment addresses a change in strategy to stop the study based on the results of a periodic review of safety data using a data cutoff date of 31-MAY-2024 that was conducted by the eDMC. At the request of the eDMC, OS data were provided for review, though there was no preplanned statistical analysis for OS. At this safety analysis, the OS Kaplan-Meier curves did not favor pembrolizumab + lenvatinib versus SOC chemotherapy.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 1.1, Synopsis	Hypotheses, Objectives, and Endpoints: A note has been added (in alignment with the study-specific investigator letter dated 05-SEP-2024) with information regarding the results of a periodic review of safety data, the subsequent decision of the Sponsor to discontinue the combination of lenvatinib + pembrolizumab (Arm 1) and lenvatinib monotherapy (Arm 3) from the study, and which analyses will or will not be conducted going forward. It also includes instructions for discontinuation of study interventions and a high-level summary of the modified protocol study procedures to be implemented as a result of the decision to terminate the study.	These changes were made to address a change in strategy to stop the study based on the results of a periodic review of safety data using a data cutoff date of 31-MAY-2024 that was conducted by the eDMC. At the request of the eDMC, OS data were provided for review, though there was no preplanned statistical analysis for OS. At this safety analysis, the OS Kaplan-Meier curves did not favor pembrolizumab + lenvatinib versus SOC chemotherapy.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
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.
Section 1.1, Synopsis	Overall Design: Updated estimated duration of study to 5 years from the time of consent of first participant or legally acceptable representative until last contact.	To align with current projections for the study completion date.
	Initial Treatment: Added text clarifying that participants in the SOC chemotherapy arm or lenvatinib monotherapy arm may not crossover to receive lenvatinib + pembrolizumab at the time of disease progression.	Refer to the rationale for primary reason for amendment.
	Second Course: Removed information on Second Course and added a note that this section is no longer applicable.	Refer to the rationale for primary reason for amendment.
	End of Treatment: Added information on extension study.	To give study participants who are discontinued the option to enroll in an extension study with pembrolizumab in combination with lenvatinib or lenvatinib monotherapy.
	Study Governance Committees: Added a note below the table clarifying that the Executive Oversight Committee and Data Monitoring Committee are no longer applicable.	Refer to the rationale for primary reason for amendment.
Section 1.2, Schema	Figure 1: Added text to footnotes clarifying that participants in the SOC chemotherapy arm or lenvatinib monotherapy arm may not crossover to receive lenvatinib + pembrolizumab at the time of disease progression.	Refer to the rationale for primary reason for amendment.
	Figure 2: Deleted this figure for Second Course.	Refer to the rationale for primary reason for amendment.
	Added information on extension study.	Refer to the Section 1.1 rationale regarding the extension study.
Section 1.3, Schedule of Activities	Added text to specify which activities will or will not be performed for the remaining duration of the study.	Refer to the rationale for primary reason for amendment.
Section 1.3.4, Second Course	Removed the Second Course SoA and added a note that this section is no longer applicable.	Refer to the rationale for primary reason for amendment.
Section 2.3, Benefit/Risk Assessment	Added a note explaining that the study will be discontinued based on a periodic review of safety data.	Refer to the rationale for primary reason for amendment.

Section Number and Name	Description of Change	Brief Rationale
Section 3, Hypotheses, Objectives, and Endpoints	A note has been added (in alignment with the study-specific investigator letter dated 05-SEP-2024) with information regarding the results of a periodic review of safety data, the subsequent decision of the Sponsor to discontinue the combination of lenvatinib + pembrolizumab (Arm 1) and lenvatinib monotherapy (Arm 3) from the study, and which analyses will or will not be conducted going forward. It also includes instructions for discontinuation of study interventions and a high-level summary of the modified protocol study procedures to be implemented as a result of the decision to terminate the study.	Refer to the rationale for primary reason for amendment.
Section 4.1, Overall Design	A note has been added (in alignment with the study-specific investigator letter dated 05-SEP-2024) with information regarding the results of an interim safety analysis, the subsequent decision of the Sponsor to remove the combination of lenvatinib + pembrolizumab (Arm 1) and lenvatinib monotherapy (Arm 3) from the study, and which analyses will or will not be conducted going forward. It also includes instructions for discontinuation of study interventions and a high-level summary of the modified protocol study procedures to be implemented as a result of the decision to terminate the study.	Refer to the rationale for primary reason for amendment.
	Added a statement that enrollment was completed on 05-SEP-2024.	Refer to the rationale for primary reason for amendment.
	Added text clarifying that participants in the SOC chemotherapy arm or lenvatinib monotherapy arm may not crossover to receive lenvatinib + pembrolizumab at the time of disease progression.	Refer to the rationale for primary reason for amendment.
	Removed information on Second Course and added a note that this section is no longer applicable.	Refer to the rationale for primary reason for amendment.
Section 4.3.4, Maximum Dose Exposure for This Study	Added information on discontinued study arms.	Refer to the rationale for primary reason for amendment.
	Removed information on Second Course treatment.	Refer to the rationale for primary reason for amendment.
Section 4.4, Beginning and End-of-Study Definition	Updated estimated duration of study to 5 years from first participant entered through long-term follow-up.	Refer to rationale for Section 1.1 related to estimated duration of study.
Section 6.1, Study Intervention(s) Administered	Added a note with instructions for discontinuation of study interventions.	Refer to the rationale for primary reason for amendment.
	In Table 2, updated the cetuximab intervention type from drug to biological/vaccine.	To further specify drug intervention type.

Section Number and Name	Description of Change	Brief Rationale
Section 6.5, Concomitant Therapy	Removed information on Second Course.	Refer to the rationale for primary reason for amendment.
Section 6.6, Dose Modification (Escalation/Titration/Other)	Added a note with instructions for discontinuation of study interventions.	Refer to the rationale for primary reason for amendment.
Section 6.7, Intervention After the End of the Study	Added information on extension study.	Refer to the Section 1.1 rationale regarding the extension study.
Section 7.1, Discontinuation of Study Intervention	Added language to note that the text in this section is original protocol text that was retained for reference.	Refer to the rationale for primary reason for amendment.
	Added new information that central tumor response assessments will no longer be performed, and scans will no longer be sent to the iCRO.	Refer to the rationale for primary reason for amendment.
	Added guidance for discontinuing study treatment due to RECIST 1.1 disease progression.	Refer to the rationale for primary reason for amendment.
	Added text clarifying that participants continuing lenvatinib + pembrolizumab on initial or crossover treatment may be permitted to continue treatment beyond disease progression following Sponsor consultation.	Refer to the rationale for primary reason for amendment.
	Added text clarifying that participants in the SOC chemotherapy arm or lenvatinib monotherapy arm may not crossover to receive lenvatinib + pembrolizumab at the time of disease progression.	Refer to the rationale for primary reason for amendment.
Section 8.1.1.1, General Informed Consent	Removed reference to Second Course.	Refer to the rationale for primary reason for amendment.
Section 8.1.5.2, Concomitant Medications	Removed information on Second Course.	Refer to the rationale for primary reason for amendment.
Section 8.2.1, Tumor Imaging and Assessment of Disease	Added new information that tumor response assessments by BICR will no longer be performed and scans will no longer be sent to the iCRO.	Refer to the rationale for primary reason for amendment.
Section 8.2.1.4, End of Treatment and Follow-up Tumor Scans	Added new information that tumor response assessments by BICR will no longer be performed and scans will no longer be sent to the iCRO.	Refer to the rationale for primary reason for amendment.
Section 8.2.1.5, Crossover Treatment Tumor Scans	Added new information that imaging scans will no longer be sent to the iCRO.	Refer to the rationale for primary reason for amendment.
	Added text clarifying that participants in the SOC chemotherapy arm or lenvatinib monotherapy arm may not crossover to receive lenvatinib + pembrolizumab at the time of disease progression.	Refer to the rationale for primary reason for amendment.
Section 8.2.1.6, Second Course Scans	Deleted all text in this section as Second Course treatment will not be performed.	Refer to the rationale for primary reason for amendment.

Section Number and Name	Description of Change	Brief Rationale
Section 8.2.1.7, RECIST 1.1 Assessment of Disease	Added new information that tumor response assessments by BICR will no longer be performed and scans will no longer be sent to the iCRO.	Refer to the rationale for primary reason for amendment.
Section 8.2.2, Patient Reported Outcomes	Added text to indicate that ePRO assessments will be discontinued.	Refer to the rationale for primary reason for amendment.
Section 8.4.5, Pregnancy and Exposure During Breastfeeding	Added information on partner pregnancy reporting.	Partner pregnancy reporting is required as this study contains genotoxic IMP.
Section 8.6, Pharmacokinetics	Added a statement that sample collection for PK and/or ADA, RNA analysis, and plasma/serum biomarkers has been discontinued.	Refer to the rationale for primary reason for amendment.
Section 8.8, Biomarkers	Added text to indicate biomarker sample collections have been discontinued.	Refer to the rationale for primary reason for amendment.
Section 8.10.2.2, Addition of Pembrolizumab Following Progression on Lenvatinib Monotherapy	Added text clarifying that participants in the lenvatinib monotherapy arm may not crossover to receive lenvatinib + pembrolizumab at the time of disease progression.	Refer to the rationale for primary reason for amendment.
Section 8.10.3, Second Course	Deleted all text in this section as Second Course treatment will not be performed.	Refer to the rationale for primary reason for amendment.
Section 8.10.5.1, Safety Follow-up Visit	Removed information on Second Course.	Refer to the rationale for primary reason for amendment.
Section 8.10.5.2, Efficacy Follow-up Visits	Added new information that Efficacy Follow-up Visits will be discontinued, and participants in efficacy follow-up and survival follow-up should be discontinued from the study.	Refer to the rationale for primary reason for amendment.
	Added new information that tumor response assessments by BICR will no longer be performed and scans will no longer be sent to the iCRO.	Refer to the rationale for primary reason for amendment.
	Removed information on Second Course.	Refer to the rationale for primary reason for amendment.
Section 8.10.5.3, Survival Follow-up Contacts	Added new information that Survival Follow-up Visits will be discontinued, and those participants remaining on study treatment at the time of Amendment 07 should continue to be monitored in the study through the AE reporting period.	Refer to the rationale for primary reason for amendment.
Section 9, Statistical Analysis Plan	Added a note to clarify the scope of analyses to be performed subsequent to the decision to terminate the study.	Refer to the rationale for primary reason for amendment.

Section Number and Name	Description of Change	Brief Rationale
Section 9.1, Statistical Analysis Plan Summary	CCI [redacted]	
Section 9.4.3, Patient Reported Outcome Endpoints	Removed text from this section as PRO endpoints will not be analyzed.	Refer to the rationale for primary reason for amendment.
Section 9.5.3, PRO Analysis Population	Removed this section as PRO endpoints will not be analyzed.	Refer to the rationale for primary reason for amendment.
Section 9.6.1, Statistical Methods for Efficacy Analyses	Removed information on analyses that will no longer be performed in the study.	Refer to the rationale for primary reason for amendment.
	Removed reference to Second Course treatment.	Refer to the rationale for primary reason for amendment.
Section 9.6.1.1, Overall Survival	Removed information on analyses that will no longer be performed in the study.	Refer to the rationale for primary reason for amendment.
Section 9.6.1.2, Progression-Free Survival	Removed information on analyses that will no longer be performed in the study.	Refer to the rationale for primary reason for amendment.
Section 9.6.1.3, Objective Response Rate	Removed information on analyses that will no longer be performed in the study.	Refer to the rationale for primary reason for amendment.
Section 9.6.1.5, Analysis Strategy for Key Efficacy Variables	Removed information on analyses that will no longer be performed in the study.	Refer to the rationale for primary reason for amendment.
Section 9.6.2, Statistical Methods for Safety Analyses	Removed reference to Second Course treatment.	Refer to the rationale for primary reason for amendment.
Section 9.6.3, Statistical Methods for Patient Reported Outcome Analyses	Removed this section as PRO endpoints will not be analyzed.	Refer to the rationale for primary reason for amendment.
	Former Section 9.6.4 renumbered to current Section 9.6.3.	Renumbering changes due to deletion of Section 9.6.3.
CCI [redacted]		

Section Number and Name	Description of Change	Brief Rationale
CCI		

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2, randomized, open-label three-arm clinical study to evaluate the safety and efficacy of lenvatinib (E7080/MK-7902) in combination with pembrolizumab (MK-3475) versus standard of care chemotherapy and lenvatinib monotherapy in participants with recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) that have progressed after platinum therapy and immunotherapy (PD-1/PD-L1 inhibitors) (LEAP-009)

Short Title: A Phase 2 study of lenvatinib (E7080/MK-7902) with pembrolizumab (MK-3475) versus SOC chemotherapy and lenvatinib monotherapy for R/M HNSCC after platinum therapy and immunotherapy

Acronym: LEAP-009 (E7080-G000-228)

Hypotheses, Objectives, and Endpoints:

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

Males and females with R/M HNSCC, who are at least 18 years old, and who have progressed after platinum-containing chemotherapy at any time (with or without cetuximab) and a PD 1/PD-L1 inhibitor will be enrolled in this study.

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

NOTE: Based on a periodic review of safety data (data cutoff 31-MAY-2024) for LEAP-009, OS Kaplan-Meier curves did not favor pembrolizumab + lenvatinib versus SOC chemotherapy, and it was considered that additional follow-up OS outcomes in favor of the combination are unlikely to support a clinically meaningful favorable benefit-risk ratio. The prespecified interim and final analyses of the study described in Section 9 will not be performed. Selected analyses of safety endpoints will be performed at the end of the study; there will be no further planned analyses for efficacy and ePRO endpoints. Updated analyses are described in Section 9.

In alignment with the study-specific investigator letter dated 05-SEP-2024, all participants should discontinue the combination of lenvatinib + pembrolizumab (Arm 1) or lenvatinib monotherapy (Arm 3), as applicable. On a case-by-case basis, investigators may contact the Sponsor for consideration of continuing lenvatinib plus pemrolizumab or lenvatinib monotherapy if they assess the participant is deriving clinical benefit. Treatment with SOC chemotherapy (Arm 2) can continue at the discretion of the investigator until a protocol specified discontinuation criterion is met. Participants who are continuing study treatment should follow the modified protocol study procedures as specified in this amendment.

All participants beyond the 30-day Safety Follow-up Visit in the initial treatment or Crossover treatment phases should be discontinued from the study; however, standard safety

reporting should continue, as applicable. As of Amendment 07, 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 required to be submitted to the iCRO; however, tumor imaging with investigator assessment should continue per protocol. Biomarker specimen collection is discontinued. The 30-day Safety Follow-up Visit is the last required visit.

Primary Objective	**Primary Endpoint**
Objective: to compare lenvatinib + pembrolizumab combination therapy and SOC chemotherapy with respect to OS. Hypothesis (H1): lenvatinib + pembrolizumab is superior to SOC with respect to OS.	OS: The time from randomization to death due to any cause.
Secondary Objectives	**Secondary Endpoints**
Objective: to compare lenvatinib + pembrolizumab combination therapy and SOC chemotherapy with respect to PFS per RECIST 1.1 by BICR Hypothesis (H2): lenvatinib + pembrolizumab is superior to SOC with respect to PFS per RECIST 1.1 by BICR.	PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.
Objective: to compare lenvatinib + pembrolizumab combination therapy and SOC chemotherapy with respect to ORR per RECIST 1.1 as assessed by BICR. Hypothesis (H3): lenvatinib + pembrolizumab is superior to SOC with respect to ORR per RECIST 1.1 by BICR.	Objective Response (OR): complete response (CR) or partial response (PR).
Objective: to assess the efficacy of lenvatinib + pembrolizumab combination therapy and SOC chemotherapy with respect to DOR per RECIST 1.1, by BICR.	DOR: 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 lenvatinib + pembrolizumab combination therapy, SOC chemotherapy, and lenvatinib monotherapy	-AEs -Study drug discontinuations due to AEs

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Squamous cell carcinoma of head and neck, Head and neck cancer
Population	Participants with R/M HNSCC who have progressed after platinum-containing chemotherapy at any time (with or without cetuximab) and a PD-1/PD-L1 inhibitor
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	Active Control Without Placebo
Study Blinding	Unblinded open-label
Blinding Roles	Outcomes Assessor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 400 participants will be treated. Participants will be randomized to receive lenvatinib + pembrolizumab (Arm 1), SOC chemotherapy (Arm 2), or lenvatinib monotherapy (Arm 3).

For lenvatinib + pembrolizumab and SOC chemotherapy, approximately 150 participants will be enrolled in each arm.

For the lenvatinib monotherapy arm, an interim analysis based on BICR assessment of objective response rate (ORR) will be performed after 30 participants have been randomized. The results will be reviewed by the Sponsor. If futility rules are not met in this interim analysis, a total of 100 participants will be enrolled into the lenvatinib monotherapy arm.

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	Once daily	Test Product
Arm 1	Pembrolizumab	25 mg/mL	200 mg	IV Infusion	Day 1 of each 3-week cycle	Test Product
Arm 2	Docetaxel	20 mg/mL	75 mg/m^2	IV Infusion	Day 1 of each 3-week cycle	Comparator
Arm 2	Capecitabine	150 mg 500 mg	1250 mg/m^2	Oral	BID (Twice a day) on Day 1 to 14 of each 3-week cycle	Comparator
Arm 2	Paclitaxel	6 mg/mL	80 mg/m^2	IV Infusion	Day 1, 8, and 15 of each 3-week cycle	Comparator
Arm 2	Cetuximab	2 mg/mL 5 mg/mL	400 mg/m^2 loading dose followed by 250 mg/m^2	IV Infusion	Day 1, 8, and 15 of each 3-week cycle	Comparator
Arm 3	Lenvatinib	10 mg 4 mg	24 mg	Oral	Once daily	Test Product

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	3 arms
Duration of Participation	Each participant will participate in the study from the time of providing documented informed consent through the final protocol-specified contact. The site's study team must have reviewed and submitted pre-study images that are of diagnostic quality from at least 2 dates to determine that radiographic progression has occurred per RECIST 1.1 following initiation of prior PD-1/PD-L1 inhibitor treatment. These images include, at a minimum, the baseline image for prior anti-PD-1/PD-L1 or an image showing nadir during prior anti-PD-1/PD-L1 treatment and an image showing progression on prior anti-PD-1/PD-L1 treatment (within 12 weeks of last dose of anti-PD-1/PD-L1 treatment). These pre-study images will be submitted to the iCRO to verify that the images are of diagnostic quality prior to randomization. The baseline tumor image collected during the Screening period must be also submitted to the iCRO for verification of measurable disease per RECIST 1.1 for eligibility prior to randomization. Archival or newly obtained (within 90 days prior to start of study treatment) biopsy for biomarker analysis will be required prior to randomization. **Initial Treatment:** **NOTE:** As of Amendment 07, participants in the SOC chemotherapy arm or lenvatinib monotherapy arm may not crossover to receive lenvatinib + pembrolizumab at the time of disease progression. After a Screening phase of up to 28 days, each participant meeting the study entry criteria will be randomized to receive either: • **Lenvatinib + Pembrolizumab (Arm 1):** Participants may continue receiving pembrolizumab for up to 35 cycles (approximately 2 years) or until a discontinuation criterion is met. Participants may continue receiving lenvatinib beyond the 35 cycles of pembrolizumab as per investigator-determined clinical benefit or until a discontinuation criterion is met. • **SOC chemotherapy (Arm 2):** Investigator's choice of single-agent docetaxel, paclitaxel, cetuximab, or capecitabine. Participants may continue receiving SOC chemotherapy as per investigator-determined clinical benefit or until a discontinuation criterion is met. Note: Upon centrally verified radiographic PD by RECIST 1.1, pembrolizumab and lenvatinib treatment may be initiated at the discretion of the investigator after consultation with the Sponsor and

	receiving informed consent. Participants may receive pembrolizumab alone during Crossover with Sponsor consultation. • **Lenvatinib Monotherapy (Arm 3):** Participants may continue receiving lenvatinib monotherapy as per investigator-determined clinical benefit until a discontinuation criterion is met. Note: Upon centrally verified PD by RECIST 1.1, pembrolizumab may be added to lenvatinib monotherapy, according to investigator decision with Sponsor consultation. The lenvatinib dose should be decreased to 20 mg daily or, if dose reduced to less than 20 mg, administered at the current reduced dose, when given in combination with pembrolizumab. Participants may receive pembrolizumab alone during Crossover with Sponsor consultation. Participants who discontinue lenvatinib prior to initiation of Crossover treatment will not restart lenvatinib. Note: For participants who were randomized initially to lenvatinib monotherapy, lenvatinib treatment may be continued during Crossover screening at the discretion of the investigator after consultation with the Sponsor. **Second Course:** **NOTE:** As of Amendment 07, there will be no Second Course. This section is no longer applicable. **End of Treatment:** After the end of treatment, each participant will be followed for the occurrence of AEs, spontaneously reported pregnancy and Survival Follow-up. Participants who discontinue for reasons other than centrally verified radiographic PD will have post-treatment follow-up imaging for disease status until PD is documented radiographically per RECIST 1.1 and centrally verified, initiate a non-study cancer treatment, withdraw consent, or become lost to follow-up (ie, the participant is unable to be contacted by the investigator). All participants will be followed for overall survival (OS) until death, withdrawal of consent, lost to follow-up, or the end of the study. Upon withdrawal of consent, the investigator will ask the participant if they may be contacted periodically for survival status; the participant's response will be documented in the study chart. The overall study ends when the last participant completes the last study-related telephone call or visit, withdraws consent, or is lost to follow-up. Upon study termination, participants are to be discontinued and may be enrolled in an extension study using pembrolizumab in combination with lenvatinib or lenvatinib monotherapy, if available.

Study Governance Committees:

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

Study governance considerations are outlined in Appendix 1.

As of Amendment 07, the Executive Oversight Committee and Data Monitoring Committee are no longer applicable.

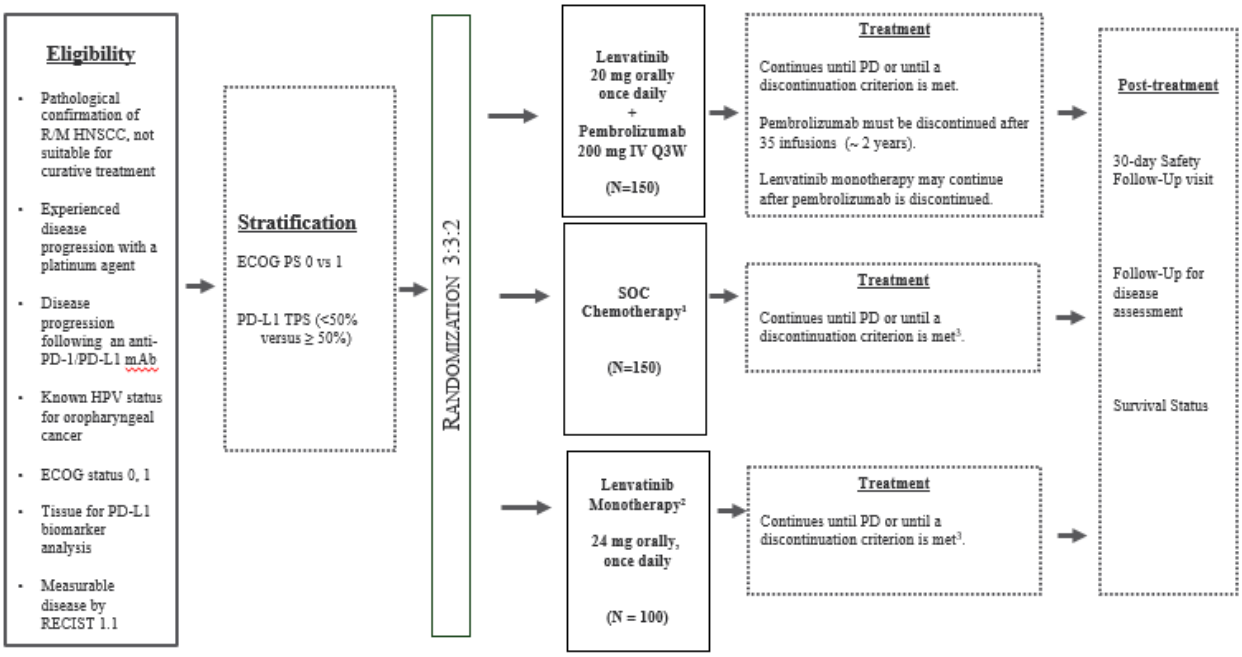
Study Accepts Healthy Participants: No

A list of abbreviations used in this document can be found in Appendix 9.

1.2 Schema

The study design is depicted in Figure 1 (Initial Treatment).

Figure 1 Initial Treatment



Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status; HPV = human papilloma virus; IA = interim analysis; IV = intravenous; mAb = monoclonal antibody; PD = progressive disease; PD-1 = programmed cell death 1; PD L1 = programmed cell death ligand-1; Q3W = every 3 weeks; R/M HNSCC = recurrent/metastatic head and neck squamous cell carcinoma; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; SOC = standard of care; TPS = tumor proportion score.

1. SOC chemotherapy= Investigator's choice of paclitaxel, docetaxel, cetuximab, or capecitabine.
   Note: Participants previously treated to one of the 4 SOC agents in this trial (i.e., docetaxel, paclitaxel, capecitabine, or cetuximab) may not receive the same agent if randomized to the SOC chemotherapy arm.
2. IA for the lenvatinib monotherapy arm will occur after 30 participants are enrolled into this arm and are followed for at least 12 weeks. Randomization will be paused for the lenvatinib monotherapy arm after the 30th participant is randomized to this arm. If number of responses is <3, enrollment for this arm will be stopped. If futility is not met at the IA, randomization to the lenvatinib monotherapy arm will be resumed*.
   *Note: The futility analysis was completed, and futility not met.
3. Participants who experience centrally verified PD in the lenvatinib monotherapy or SOC chemotherapy arms can crossover to receive lenvatinib + pembrolizumab at time of disease progression with Sponsor consultation. As of Amendment 07, participants in the SOC chemotherapy arm or lenvatinib monotherapy arm may not crossover to receive lenvatinib + pembrolizumab at the time of disease progression.

Upon study termination, participants are discontinued and may be enrolled in an extension study using pembrolizumab in combination with lenvatinib or lenvatinib monotherapy, if available.

1.3 Schedule of Activities

As of Amendment 07, participants who are still on study treatment will no longer require ePRO assessments to be performed. PK/ADA and biomarker samples (blood for genetic analyses, plasma/serum biomarker, RNA analysis, and ctNA analysis) are discontinued.

All participants who are still on study treatment 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.

Efficacy follow-up visits will no longer be conducted. Therefore, participants in efficacy follow-up and survival follow-up should be discontinued from the study.

As of Amendment 07, only the following procedures at the indicated time points are to be performed:

- Imaging: while on study treatment, EOT, Safety FU
- Physical examination; Vital signs: while on study treatment, EOT, Safety FU
- ECG, MUGA, or ECHO: while on study treatment, then Safety FU
- ECOG: while on study treatment, EOT, Safety FU
- Serum b-HCG or urine pregnancy (WOCBP only): while on study treatment, EOT, Safety FU
- Hematology/Chemistry/Urinalysis: while on study treatment, EOT, Safety FU
- Urinalysis/urine dipstick testing, as specified per protocol: while still on lenvatinib, EOT, and Safety FU
- T3 or FT3, T4, TSH: while on study treatment, then Safety FU

The full SoA tables for Arm 1, Arm 2, Arm 3, and Crossover Treatment below are retained for reference.

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

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

Study Period	**Screen-ing**	**Intervention (21-Day Cycles)**											**Post-Intervention Visit**			**Notes**
		C1			**C2**		**C3**	**C4**	**C5**	**C6 to C35**	**≥C36**	**EOT**	**Safety FU**	**Effi-cacy FU**	**Sur-vival FU**	
Visit/Cycle Number																
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Scheduling Window (Days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At D/C**	**30d after last dose (+7d)**	**Q6W (Y1) or Q9W (after Y1) (±7d)**	**Q12W (±14d)**	**All procedures/assessments performed before administration of study intervention unless otherwise indicated.**
Administrative Procedures																
Informed Consent	X															Documented informed consent must be obtained prior to performing any protocol-specific procedures. If the investigator plans to treat beyond centrally verified radiographic disease progression, additional consent is required.
Inclusion/Exclusion Criteria	X															AJCC v8 should be used for clinical evaluation and staging of participant's tumor burden at initial diagnosis and at Screening.
Participant Identification Card	X	X*														* Update at C1D1 with randomization number.
Demographics and Medical History	X															Includes smoking and tobacco use.

Study Period	Screen-ing	Intervention (21-Day Cycles)											Post-Intervention Visit			Notes
		C1			C2		C3	C4	C5	C6 to C35	≥C36	EOT	Safety FU	Effi-cacy FU	Sur-vival FU	
Visit/Cycle Number																
Cycle Day		1	8	15	1	15	1	1	1	1	1					
Prior/Concomitant Medication Review	◄	—	—	—	—	—	—	—	—	—	—	—	►			Medications received within 30 days before the first dose of study intervention through 30 days after the last dose of study intervention or 90 days if used to treat an SAE or 30 days after last dose if participant starts a new antineoplastic therapy, whichever is sooner.
Prior Anticancer Therapies for Treatment of HNSCC	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.
Subsequent Anticancer Treatment												X	X	X	X	All anticancer therapy will be recorded until the time of death or termination of survival FU. If a clinic visit is not feasible, follow-up information may be obtained by telephone, email or from other sources.

Study Period	Screen-ing	Intervention (21-Day Cycles)											Post-Intervention Visit			Notes
		C1			C2		C3	C4	C5	C6 to C35	≥C36	EOT	Safety FU	Effi-cacy FU	Sur-vival FU	
Visit/Cycle Number																
Cycle Day		1	8	15	1	15	1	1	1	1	1					
Survival Status		◄———	———	———	———	———	———	———	———	———	———►				X	Survival Follow-up continues after centrally verified PD, after discontinuation of study intervention, and after the start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Study Intervention Administration																
Lenvatinib Dispensing		X			X		X	X	X	X	X					Collect and record the number of lenvatinib capsules returned.
Lenvatinib Administration		X*	X	X*	X*	X	X	X	X	X	X					* Lenvatinib will be given in the clinic on C1D1, C1D15, and C2D1 Participants randomized to lenvatinib + pembrolizumab should be given lenvatinib within 0 to 4 hours after completion of pembrolizumab infusion on C1D1 and C2D1. On C1D15 the dose of lenvatinib will be given in the clinic within 2 hours prior to the lenvatinib postdose PK blood sample. Participants will self – administer lenvatinib on all other days.

Study Period	Screen-ing	Intervention (21-Day Cycles)											Post-Intervention Visit			Notes
		C1			C2		C3	C4	C5	C6 to C35	≥C36	EOT	Safety FU	Effi-cacy FU	Sur-vival FU	
Visit/Cycle Number																
Cycle Day		1	8	15	1	15	1	1	1	1	1					
Pembrolizumab Administration		X			X		X	X	X	X						For participants randomized to lenvatinib + pembrolizumab study intervention only. After C1D1, pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each subsequent cycle due to administrative reasons.
Efficacy Procedures/Assessments																
Submission of Pre-study Imaging	X															Diagnostic quality pre-study images from ≥2 dates must have been reviewed at site to determine radiographic progression per RECIST 1.1 following initiation of pre-study anti-PD-1/PD-L1 agent. The iCRO must have received these scans and have verified that they are of diagnostic quality prior to randomization.
Tumor Imaging (head and neck, chest and abdomen) and Response Assessment **Note:** Imaging of the brain and pelvis are optional (if clinically indicated).	X						X		X	X*		X		X		Imaging should be performed at Screening, Week 6 (42-49 days) from the date of randomization. * After Week 6 imaging every 6 weeks (±7 days) for 1 year (48 weeks). After 1 year (48 weeks), imaging will occur every 9 weeks (±7 days). Schedule should be followed regardless of treatment delays. Follow-up imaging will use the same imaging schedule used while on study intervention calculated from the date of randomization.

Study Period	Screen-ing	Intervention (21-Day Cycles)											Post-Intervention Visit			Notes
		C1			C2		C3	C4	C5	C6 to C35	≥C36	EOT	Safety FU	Effi-cacy FU	Sur-vival FU	
Visit/Cycle Number																
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Safety Procedures/Assessments																
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. * Report Pregnancy 120 days following pembrolizumab or 30 days following cessation of lenvatinib, whichever occurs last.
Full Physical Examination	X											X				Full physical examination to be performed within 10 days prior to start of study intervention.
Height	X															
Directed Physical Examination		X		X	X	X	X	X	X	X	X		X			
Telephone Contact			X													**A phone visit will be scheduled to report blood pressure and record AEs. Blood pressure will be taken, for example, at home or at a local pharmacy, and will be reviewed with the investigator or designee.**
Vital Signs (resting BP, heart rate, respiratory rate, and temp) and weight	X	X		X*	X	X*	X	X	X	X	X	X	X			*** The D15 visits are mandatory for C1 and C2.** During C3 and subsequent cycles, participants may return for the D15 visit if BP monitoring is required.

Study Period	Screen-ing	Intervention (21-Day Cycles)											Post-Intervention Visit			Notes
		C1			C2		C3	C4	C5	C6 to C35	≥C36	EOT	Safety FU	Effi-cacy FU	Sur-vival FU	
Visit/Cycle Number																
Cycle Day		1	8	15	1	15	1	1	1	1	1					
12-lead ECG with QTcF Determination	X	X			X					X*	X*	X	X			ECG at Screening, C1D1, C2D1, * D1 of every 4th cycle (12 weeks) thereafter (eg, C6, C10, C14, etc.), EOT, and safety follow-up. ECG at C1D1 and C2D1 should be performed approximately 2 hours post-lenvatinib dose. For high-risk participants (as defined in lenvatinib product label), conduct ECG monitoring every cycle. Additional time points may be performed as clinically necessary. If lenvatinib is discontinued, ECGs are only required at the EOT and Safety FU visits.
MUGA or ECHO Scan	X												X			Additional LVEF assessments may be performed as clinically indicated.
ECOG Performance Status	X	X*			X		X	X	X	X	X	X	X			At Screening, obtain within 7 days before initiation of study intervention and then on D1 of each cycle prior to dosing. ECOG will need to be repeated if the assessment was performed outside of the protocol window. * If screening ECOG performance status is obtained within 3 days prior to C1D1, no need to repeat at C1D1.

Study Period	Screen-ing	Intervention (21-Day Cycles)											Post-Intervention Visit			Notes
		C1			C2		C3	C4	C5	C6 to C35	≥C36	EOT	Safety FU	Effi-cacy FU	Sur-vival FU	
Visit/Cycle Number																
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**					
Laboratory Procedures/Assessments (Local Laboratory)																
Serum β-HCG or Urine Pregnancy (WOCBP only)	X				X		X	X	X	X	X	X	X			WOCBP require negative test prior to randomization. If more than 24 hours have elapsed prior to first dose of study intervention, another pregnancy test is required prior to starting study intervention. A serum or urine pregnancy test will be performed per Appendix 2.
HIV, Hepatitis B, and Hepatitis C	X															Required at baseline only if mandated by local health authority.
Serum FSH (WONCBP only)	X															In the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in postmenopausal range is required.
CBC with Differential	X*			X	X		X	X	X	X	X	X	X			* Perform within 7 days before first dose. After C1D1, collect samples within 3 days before dosing.
Clinical Chemistry	X*			X	X		X	X	X	X	X	X	X			

Study Period	Screen-ing	Intervention (21-Day Cycles)											Post-Intervention Visit			Notes
		C1			C2		C3	C4	C5	C6 to C35	≥C36	EOT	Safety FU	Effi-cacy FU	Sur-vival FU	
Visit/Cycle Number																
Cycle Day		1	8	15	1	15	1	1	1	1	1					
Urine Dipstick Testing (or Urinalysis)	X*			X	X	X	X	X	X	X	X	X				* Perform within 7 days before first dose. Urine dipstick testing for participants with proteinuria ≥2+ should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles. If lenvatinib is discontinued, urine dipstick testing is no longer required. After Screening, urine dipstick-testing for protein will be performed within 3 days before Day 1 of every cycle while participants are taking lenvatinib.
Urinalysis	X									X		X	X			Perform within 7 days before first dose. During study intervention obtain urinalysis at every 6th cycle (eg, 6, 12, 18, etc.), within 3 days of dosing.
INR or PT and aPTT or PTT	X*															* Perform screening labs within 7 days prior to the first dose. Additional testing is to be performed as clinically indicated for participants taking anticoagulants.

Study Period	Screen-ing	Intervention (21-Day Cycles)											Post-Intervention Visit			Notes
		C1			C2		C3	C4	C5	C6 to C35	≥C36	EOT	Safety FU	Effi-cacy FU	Sur-vival FU	
Visit/Cycle Number																
Cycle Day		1	8	15	1	15	1	1	1	1	1					
T3 or FT3, T4, TSH	X*				X			X		X	X		X			* Perform screening labs within 7 days prior to the first dose, then within 3 days before dosing on subsequent cycles. Perform at C2 and every 2 cycles thereafter (C4, C6, C8, etc.). Participants may be dosed in subsequent cycles after C1D1 while thyroid function test are pending. Free T3/T4 is acceptable if total T3/T4 cannot be determined. The central laboratory may be used only if the local laboratory cannot perform these tests.
Pharmacokinetics/Pharmacodynamics/ Biomarkers (Central Laboratory)																
Serum for Pembrolizumab PK		X			X					X*						PK samples will be collected from Arm 1 (lenvatinib + pembrolizumab). Collect predose on C1D1, C2D1, and *C8D1.
Serum Anti-pembrolizumab Antibodies (ADA)		X			X					X*						ADA samples will be collected from Arm 1 (lenvatinib + pembrolizumab). Collect predose on C1D1, C2D1, and *C8D1.

Study Period	Screen-ing	Intervention (21-Day Cycles)											Post-Intervention Visit			Notes
		C1			C2		C3	C4	C5	C6 to C35	≥C36	EOT	Safety FU	Effi-cacy FU	Sur-vival FU	
Visit/Cycle Number																
Cycle Day		1	8	15	1	15	1	1	1	1	1					
Plasma for Lenvatinib PK		X		X	X											Lenvatinib PK samples will be collected from both Arms 1 and 3 (lenvatinib + pembrolizumab and lenvatinib monotherapy) C1D1: postdose at any time from 0.5 to 4h, collection from 6 to 10h postdose is optional. C1D15: collect predose within 2h of lenvatinib dosing and postdose at any time from 2 to 12h postdose. C2D1: collect predose within 2h of lenvatinib dosing and postdose at any time from 0.5 to 4h, collection from 6 to 10h postdose is optional. Note: Postdose samples will not be collected if lenvatinib dosing is on hold due to dose modifications, etc.
Tissue Collection for Participants with Oropharynx Cancer (Tested Centrally or Locally for HPV status)	X															Archival or newly obtained (within 90 days prior to start of study treatment) tumor specimen for HPV status only if prior results are not available.
Tissue Collection for Biomarker Analysis (Tested Centrally)	X															Archival or newly obtained (within 90 days prior to start of study treatment) tumor specimen. Should be submitted to the central laboratory before randomization.

Study Period	Screen-ing	Intervention (21-Day Cycles)											Post-Intervention Visit			Notes
		C1			C2		C3	C4	C5	C6 to C35	≥C36	EOT	Safety FU	Effi-cacy FU	Sur-vival FU	
Visit/Cycle Number																
Cycle Day		1	8	15	1	15	1	1	1	1	1					
Blood for Genetic Analyses		X														Collect predose. See Section 8.8 for additional information.
Blood for Plasma Biomarkers		X			X		X		X	X	X	X				Collect at predose on D1 of C1, C2, C3, C5, C7, C9, C11, C13, C15, C17, then on D1 of every 3 cycles until EOT, including at the EOT visit.
Blood for Serum Biomarkers		X		X	X		X		X			X				Collect predose. Collect on C1D1, C1D15, C2D1, C3D1, C5D1, and at EOT.
Blood for RNA Analysis		X			X		X		X			X				Collect predose on C1D1, C2D1, C3D1, C5D1, and at EOT.
Blood for Circulating Tumor Nucleic Acids		X			X		X		X	X	X	X				Collect at predose on D1 of C1, C2, C3, C5, C7, C9, C11, C13, C15, C17, then on D1 of every 3 cycles until EOT, including at the EOT visit.

Study Period	Screening	Intervention (21-Day Cycles)											Post-Intervention Visit			Notes
		C1			C2		C3	C4	C5	C6 to C35	≥C36	EOT	Safety FU	Efficacy FU	Survival FU	
Visit/Cycle Number																
Cycle Day		1	8	15	1	15	1	1	1	1	1					
Patient reported Outcomes (PRO)*																
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. * Obtain on Day 1 of every cycle from C1 through C9, then Day 1 of every other cycle through C17 (C9, C11, C13, C15, C17), then collect every 3 cycles through C35 (C20, C23, C26, C29, C32, C35). Obtain at EOT and Safety FU. Refer to 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			

Abbreviations: ADA = anti-drug antibodies (pembrolizumab); AE = adverse event; AJCC = American Joint Committee on Cancer; aPTT = activated partial thromboplastin time; BP = blood pressure; β-HCG; = β human chorionic gonadotropin; C = cycle; CBC = complete blood count; CXDY= Cycle X Day Y; d = days; D = day; D/C = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ECHO = echocardiogram; EORTC = European Organization for Research and Treatment of Cancer; EOT = end of treatment; ePRO = electronic patient reported outcome; EQ-5D-5L = European Quality of Life Five-Dimensional Five-Level Scale Questionnaire; FSH = follicle-stimulating hormone; FT3 = free triiodothyronine; FU = follow-up; h = hours; HIV = human immunodeficiency virus; HNSCC = head and neck squamous cell carcinoma; HPV = human papilloma virus; iCRO = imaging clinical research organization; INR = international normalized ratio; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition; PD = progressive disease; PD-1 = programmed cell death 1; PD-L1 = programmed cell death ligand 1; PK = pharmacokinetics; PRO = patient reported outcome; PT = prothrombin time; PTT = partial 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; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; RNA= ribonucleic acid; SAE = serious adverse event; SoA = schedule of activities; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential; WONCBP = women of non-childbearing potential; Y = year.

1.3.2 Initial Treatment: SOC Chemotherapy (Arm 2)

Note: **Participants receiving Capecitabine or Docetaxel will not have visits/procedures on Day 8 or Day 15.**

Study Period	**Screen-ing**	**SOC Chemotherapy Intervention (21-Day Cycles)**													**Post-Intervention Visit**			**Notes**
		C1			**C2**			**C3**			**≥C4**			**EOT**	**Safety FU**	**Effi-cacy FU**	**Sur-vival FU**	
Visit/Cycle Number																		
Cycle Day		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**					
Scheduling Window (Days)	**-28 to -1**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**At D/C**	**30d after last dose (+7d)**	**Q6W (Y1) or Q9W (Y2+) (±7d)**	**Q12W (±14d)**	**All procedures/assessments performed before administration of study intervention unless otherwise indicated.**
Administrative Procedures																		
Informed Consent	X																	Documented informed consent must be obtained prior to performing any protocol-specific procedures. If the investigator plans to treat beyond centrally verified radiographic disease progression, additional consent is required.
Inclusion/Exclusion Criteria	X																	AJCC v8 should be used for clinical evaluation and staging of participant's tumor burden at initial diagnosis and at Screening.
Participant Identification Card	X	X*																* Update at C1D1 with randomization number.

Study Period	**Screen-ing**	**SOC Chemotherapy Intervention (21-Day Cycles)**													**Post-Intervention Visit**			**Notes**
		C1			**C2**			**C3**			**≥C4**			**EOT**	**Safety FU**	**Effi-cacy FU**	**Sur-vival FU**	
Visit/Cycle Number																		
Cycle Day		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**					
Demographics and Medical History	X																	
Prior/ Concomitant Medication Review	◄———	———	———	———	———	———	———	———	———	———	———	———	———	———	———►			Medications received within 30 days before the first dose of study intervention through 30 days after the last dose of study intervention or 90 days if used to treat an SAE or 30 days after last dose if participant starts a new antineoplastic therapy, whichever is sooner.
Prior Anticancer Therapies for Treatment of HNSCC	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	Screen-ing	SOC Chemotherapy Intervention (21-Day Cycles)													Post-Intervention Visit			Notes
		C1			C2			C3			≥C4			EOT	Safety FU	Effi-cacy FU	Sur-vival FU	
Visit/Cycle Number																		
Cycle Day		1	8	15	1	8	15	1	8	15	1	8	15					
Subsequent Anticancer Treatment														X	X	X	X	All anticancer therapy will be recorded until the time of death or termination of survival FU. If a clinic visit is not feasible, follow-up information may be obtained by telephone, email or from other sources.
Survival Status		◄———											———►				X	Survival follow-up continues after centrally verified PD, after discontinuation of study intervention and after the start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.

Study Period	Screen-ing	SOC Chemotherapy Intervention (21-Day Cycles)													Post-Intervention Visit			Notes
		C1			C2			C3			≥C4			EOT	Safety FU	Effi-cacy FU	Sur-vival FU	
Visit/Cycle Number																		
Cycle Day		1	8	15	1	8	15	1	8	15	1	8	15					
Study Intervention Administration																		
SOC Chemotherapy																		
Docetaxel		X			X			X			X							Docetaxel 75 mg/m^2: Day 1 of each 21-day cycle. Participants receiving docetaxel will not have visits/procedures on Day 8 or Day 15.
Paclitaxel		X	X	X	X	X	X	X	X	X	X	X	X					Paclitaxel 80 mg/m^2: Days 1, 8, and 15 of each 21-day cycle.
Cetuximab		X	X	X	X	X	X	X	X	X	X	X	X					Cetuximab 400 mg/m^2 loading dose followed by 250 mg/m^2: Days 1, 8, and 15 of each 21-day cycle.
Capecitabine		X			X			X			X							Capecitabine 1250 mg/m^2 BID on Days 1 to 14 of each 21-day cycle, followed by a rest period of 1 week. Participants will self – administer capecitabine. Participants receiving capecitabine will not have visits/procedures on Day 8 or Day 15.

Study Period	Screen-ing	SOC Chemotherapy Intervention (21-Day Cycles)													Post-Intervention Visit			Notes
		C1			C2			C3			≥C4			EOT	Safety FU	Effi-cacy FU	Sur-vival FU	
Visit/Cycle Number																		
Cycle Day		1	8	15	1	8	15	1	8	15	1	8	15					
Efficacy Procedures/Assessments																		
Submission of Pre-study Imaging	X																	Diagnostic quality pre-study images from ≥2 dates must have been reviewed at site to determine radiographic progression per RECIST 1.1 following initiation of pre-study anti-PD-1/PD-L1 agent. The iCRO must have received these scans and have verified that they are of diagnostic quality prior to randomization.

Study Period	Screen-ing	SOC Chemotherapy Intervention (21-Day Cycles)													Post-Intervention Visit			Notes
		C1			C2			C3			≥C4			EOT	Safety FU	Effi-cacy FU	Sur-vival FU	
Visit/Cycle Number																		
Cycle Day		1	8	15	1	8	15	1	8	15	1	8	15					
Tumor Imaging (head and neck, chest and abdomen) and Response Assessment **Note**: Imaging of the brain and pelvis are optional (if clinically indicated).	X							X					X*	X		X		Imaging should be performed at Screening, Week 6 (42-49 days) from the date of randomization. * After Week 6 imaging every 6 weeks (±7 days). After 1 year (48 weeks), imaging will occur every 9 weeks (±7 days). Schedule should be followed regardless of treatment delays. Follow-up imaging will use the same imaging schedule used while on study intervention calculated from the date of randomization.
Safety Procedures/Assessments																		
AE/SAE review	X	X	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.
Full Physical Examination	X													X				Full physical examination to be performed within 10 days prior to start of study intervention.
Height	X																	

Study Period	Screen-ing	SOC Chemotherapy Intervention (21-Day Cycles)													Post-Intervention Visit			Notes
		C1			C2			C3			≥C4			EOT	Safety FU	Effi-cacy FU	Sur-vival FU	
Visit/Cycle Number																		
Cycle Day		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**					
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X	X		X			
Vital Signs (resting BP, heart rate, respiratory rate, and temp) and weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
12-lead ECG with QTcF Determination	X																	
MUGA or ECHO Scan	X																	Additional LVEF assessments may be performed as clinically indicated.
ECOG Performance Status	X	X*			X			X			X			X	X			At Screening, obtain within 7 days before initiation of study intervention and then on D1 of each cycle prior to dosing. ECOG will need to be repeated if the assessment was performed outside of the protocol window. * If screening ECOG performance status is obtained within 3 days prior to C1D1, no need to repeat at C1D1.

Study Period	Screen-ing	SOC Chemotherapy Intervention (21-Day Cycles)													Post-Intervention Visit			Notes
		C1			C2			C3			≥C4			EOT	Safety FU	Effi-cacy FU	Sur-vival FU	
Visit/Cycle Number																		
Cycle Day		1	8	15	1	8	15	1	8	15	1	8	15					
Laboratory Procedures/Assessments (Local Laboratory)																		
Serum β-HCG or Urine Pregnancy (WOCBP only)	X				X			X			X			X	X			WOCBP require negative test prior to randomization. If more than 24 hours have elapsed prior to first dose of study intervention, another pregnancy test is required prior to starting study intervention. A serum or urine pregnancy test will be performed per Appendix 2. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required.
HIV, Hepatitis B, and Hepatitis C	X																	Required at baseline only if mandated by local health authority.
Serum FSH (WONCBP only)	X																	In the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in postmenopausal range is required.
CBC with Differential	X*		X	X	X	X	X	X	X	X	X	X	X	X	X			* Perform within 7 days before first dose. After C1D1, collect samples within 3 days before dosing.
Clinical Chemistry	X*		X	X	X	X	X	X	X	X	X	X	X	X	X			

Study Period	Screen-ing	SOC Chemotherapy Intervention (21-Day Cycles)													Post-Intervention Visit			Notes
		C1			C2			C3			≥C4			EOT	Safety FU	Effi-cacy FU	Sur-vival FU	
Visit/Cycle Number																		
Cycle Day		1	8	15	1	8	15	1	8	15	1	8	15					
Urine Dipstick Testing	X																	Perform within 7 days before first dose.
Urinalysis	X										X			X	X			Perform within 7 days before first dose. During study intervention obtain urinalysis at every 6th cycle (eg, 6, 12, 18, etc.), within 3 days of dosing.
INR or PT and aPTT or PTT	X*																	* Perform within 7 days prior to first dose in C1. Additional testing to be conducted as clinically indicated for participants taking anticoagulants.
T3 or FT3, T4, TSH	X*				X						X				X			* Perform screening labs within 7 days prior to the first dose, then within 3 days before dosing on subsequent cycles. Perform at C2 and every 2 cycles thereafter (C4, C6, C8, etc.). Participants may be dosed in subsequent cycles after C1D1 while thyroid function test are pending. Free T3 is acceptable if T3 cannot be determined. The central laboratory may be used only if the local laboratory cannot perform these tests.

Study Period	Screen-ing	SOC Chemotherapy Intervention (21-Day Cycles)													Post-Intervention Visit			Notes
		C1			C2			C3			≥C4			EOT	Safety FU	Effi-cacy FU	Sur-vival FU	
Visit/Cycle Number																		
Cycle Day		1	8	15	1	8	15	1	8	15	1	8	15					
Pharmacokinetics/Pharmacodynamics/ Biomarkers (Central Laboratory)																		
Tissue Collection for Participants with Oropharynx Cancer (Tested Centrally or Locally for HPV status)	X																	Archival or newly obtained (within 90 days prior to start of study treatment) tumor specimen for HPV status only if prior results are not available.
Tissue Collection for Biomarker Analysis (Tested Centrally)	X																	Archival or newly obtained (within 90 days prior to start of study treatment) tumor specimen. Tissue should be submitted to the central laboratory before randomization.
Blood for Genetic Analyses		X																Collect predose. See Section 8.8 for additional information.
Blood for Plasma Biomarkers		X			X			X			X			X				Collect at predose on D1 of C1, C2, C3, C5, C7, C9, C11, C13, C15, C17, then on D1 of every 3 cycles until EOT, including at the EOT visit.

Study Period	Screen-ing	SOC Chemotherapy Intervention (21-Day Cycles)													Post-Intervention Visit			Notes
		C1			C2			C3			≥C4			EOT	Safety FU	Effi-cacy FU	Sur-vival FU	
Visit/Cycle Number																		
Cycle Day		1	8	15	1	8	15	1	8	15	1	8	15					
Blood for Serum Biomarkers		X		X	X			X			X*			X				Collect predose. Collect on C1D1, C1D15, C2D1, C3D1, *C5D1, and at EOT.
Blood for RNA Analysis		X			X			X			X*			X				Collect predose on C1D1, C2D1, C3D1, *C5D1, and at EOT.
Blood for Circulating Tumor Nucleic Acids		X			X			X			X			X				Collect at predose on D1 of C1, C2, C3, C5, C7, C9, C11, C13, C15, C17, then on D1 of every 3 cycles until EOT, including at the EOT visit.

Study Period	Screen-ing	SOC Chemotherapy Intervention (21-Day Cycles)													Post-Intervention Visit			Notes
		C1			C2			C3			≥C4			EOT	Safety FU	Effi-cacy FU	Sur-vival FU	
Visit/Cycle Number																		
Cycle Day		1	8	15	1	8	15	1	8	15	1	8	15					
Patient reported Outcomes (PRO)*																		
EQ-5D-5L		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. * Obtain on Day 1 of every cycle from C1 through C9, then Day 1 of every other cycle through C17 (C9, C11, C13, C15, C17), then collect every 3 cycles through C35 (C20, C23, C26, C29, C32, C35). Obtain at EOT and Safety FU. Refer to Section 8.2.2.
EORTC QLQ-C30		X			X			X			X*			X	X			
EORTC QLQ-H&N35		X			X			X			X*			X	X*			

Abbreviations: AE = adverse event; AJCC = American Joint Committee on Cancer; aPTT = activated partial thromboplastin time; BID = twice daily; BP = blood pressure; β-HCG; = β human chorionic gonadotropin; C = cycle; CBC = complete blood count; CXDY= Cycle X Day Y; d = days; D = day; D/C = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ECHO = echocardiogram; EORTC = European Organization for Research and Treatment of Cancer; EOT = end of treatment; ePRO = electronic patient reported outcome;; 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; HPV = human papilloma virus; iCRO = imaging clinical research organization; INR = international normalized ratio; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition; PD = progressive disease; PD-1 = programmed cell death 1; PD-L1 = programmed cell death ligand 1;PRO = patient reported outcome; PT = prothrombin time; PTT = partial 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; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; RNA= ribonucleic acid; SAE = serious adverse event; SoA = schedule of activities; SOC = standard of care; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential; WONCBP = women of non-childbearing potential; Y = year.

1.3.3 Crossover Treatment

NOTE: If all required assessments are performed within specified windows of Crossover C1D1, Screening visit for Crossover is not required.

Study Period	Crossover Screening	Intervention (21-Day Cycles)											Post-Intervention Visit			Notes
Visit/Cycle Number		C1			C2		C3	C4	C5	C6 to C35	≥C36	EOT	Safety FU	Efficacy FU	Survival FU	
Cycle Day		1	8	15	1	15	1	1	1	1	1					
Scheduling Window (Days)	-28 to -1	+3	±3	±3	±3	+3	±3	±3	±3	±3	±3	At D/C	30d after last dose (+7d)	Q6W (Y1) or Q9W (Y2+) (±7d)	Q12W (±14d)	All procedures/assessments performed before administration of study intervention unless otherwise indicated.
Administrative Procedures																
Prior/Concomitant Medication Review	◄———	———	———	———	———	———	———	———	———	———	———	———►				Medications received within 30 days before the first dose of study intervention through 30 days after the last dose of study intervention or 90 days if used to treat an SAE or 30 days after last dose if participant starts a new antineoplastic therapy, whichever is sooner.
Subsequent Anticancer Treatment												X	X	X	X	All anticancer therapy will be recorded until the time of death or termination of survival FU. If a clinic visit is not feasible, follow-up information may be obtained by telephone, email or from other sources.

Study Period	Crossover Screening	Intervention (21-Day Cycles)											Post-Intervention Visit			Notes
		C1			C2		C3	C4	C5	C6 to C35	≥C36	EOT	Safety FU	Efficacy FU	Survival FU	
Visit/Cycle Number																
Cycle Day		1	8	15	1	15	1	1	1	1	1					
Survival Status		◄———	———	———	———	———	———	———	———	———	———	———			X	Survival follow-up continues after centrally verified PD, after discontinuation of study intervention and after the start of new anticancer treatment. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Study Intervention Administration																
Lenvatinib Dispensing		X			X		X	X	X	X	X					Collect and record number of lenvatinib capsules returned.
Lenvatinib Administration		X*	X	X*	X*	X	X	X	X	X	X					* Lenvatinib will be given in the clinic on C1D1, C1D15, and C2D1 Participants receiving lenvatinib + pembrolizumab should be given lenvatinib within 0 to 4 hours after completion of pembrolizumab infusion on C1D1 and C2D1. On C1D15 the dose of lenvatinib will be given in the clinic within 2 hours prior to the lenvatinib postdose PK blood sample. Participants will self – administer lenvatinib on all other days.
Pembrolizumab Administration		X			X		X	X	X	X						Crossover C1D15 and C2D15 visits are not required for patients initiating crossover treatment with pembrolizumab alone.

Study Period	Crossover Screening	Intervention (21-Day Cycles)											Post-Intervention Visit			Notes
Visit/Cycle Number		C1			C2		C3	C4	C5	C6 to C35	≥C36	EOT	Safety FU	Efficacy FU	Survival FU	
Cycle Day		1	8	15	1	15	1	1	1	1	1					
Efficacy Procedures/Assessments																
Tumor Imaging (head and neck, chest and abdomen) and Response Assessment **Note:** Imaging of the brain and pelvis are optional (if clinically indicated).	X						X		X	X*		X		X		Imaging should be performed at Screening (a new baseline within 28 days of C1D1 will be needed [this can be the centrally verified PD scan if it's within the 28-day window]), Week 6 (42-49 days) from the date of C1D1 * After Week 6 imaging every 6 weeks (±7 days) for 1 year (48 weeks). After 1 year (48 weeks), imaging will occur every 9 weeks (±7 days). Schedule should be followed regardless of treatment delays. Follow-up imaging will use the same imaging schedule used while on study intervention calculated from the date of Crossover C1D1.
Safety Procedures/Assessments																
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. * Report Pregnancy 120 days following pembrolizumab or 30 days following cessation of lenvatinib, whichever occurs last.
Full Physical Examination	X											X				Full physical examination to be performed within 10 days prior to start of study intervention.
Height	X															

Study Period	Crossover Screening	Intervention (21-Day Cycles)											Post-Intervention Visit			Notes
		C1			C2		C3	C4	C5	C6 to C35	≥C36	EOT	Safety FU	Efficacy FU	Survival FU	
Visit/Cycle Number																
Cycle Day		1	8	15	1	15	1	1	1	1	1					
Directed Physical Examination		X		X	X	X	X	X	X	X	X		X			
Telephone Contact			X													**A phone visit will be scheduled to report blood pressure and record AEs. Blood pressure will be taken, for example, at home or at a local pharmacy, and will be reviewed with the investigator or designee.**
Vital Signs (resting BP, heart rate, respiratory rate, and temp) and weight	X	X		X *	X	X *	X	X	X	X	X	X	X			* **The D15 visits are mandatory for C1 and C2.** During C3 and subsequent cycles, participants may return for the D15 visit if BP monitoring is required.
12-lead ECG with QTcF Determination	X	X			X					X*	X*	X	X			ECG at Screening, C1D1, C2D1. * D1 of every 4th cycle (12 weeks) thereafter (eg, C6, C10, C14, etc.), EOT, and safety follow-up. ECG at C1D1 and C2D1 should be performed approximately 2 hours post-lenvatinib dose. For high-risk participants (as defined in lenvatinib product label), conduct ECG monitoring every cycle. Additional time points may be performed as clinically necessary. If lenvatinib is discontinued, ECGs are only required at the EOT and Safety FU visits.

Study Period	Crossover Screening	Intervention (21-Day Cycles)											Post-Intervention Visit			Notes
		C1			C2		C3	C4	C5	C6 to C35	≥C36	EOT	Safety FU	Efficacy FU	Survival FU	
Visit/Cycle Number																
Cycle Day		1	8	15	1	15	1	1	1	1	1					
ECOG Performance Status	X	X*			X		X	X	X	X	X	X	X			At screening, obtain within 7 days before initiation of study intervention and then on D1 of each cycle prior to dosing. ECOG will need to be repeated if the assessment was performed outside of the protocol window. * If screening ECOG performance status is obtained within 3 days prior to Crossover C1D1, no need to repeat at C1.
Laboratory Procedures/Assessments (Local Laboratory)																
Serum β-HCG or Urine Pregnancy (WOCBP only)	X				X		X	X	X	X	X	X	X			WOCBP require negative test prior to Crossover C1D1. If more than 24 hours have elapsed prior to first dose of study intervention, another pregnancy test is required prior to starting study intervention. A serum or urine pregnancy test will be performed per Appendix 2.
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	Crossover Screening	Intervention (21-Day Cycles)											Post-Intervention Visit			Notes
		C1			C2		C3	C4	C5	C6 to C35	≥C36	EOT	Safety FU	Efficacy FU	Survival FU	
Visit/Cycle Number																
Cycle Day		1	8	15	1	15	1	1	1	1	1					
CBC with Differential	X*			X	X		X	X	X	X	X	X	X			* Perform within 7 days before first dose. After C1D1, collect samples within 3 days before dosing.
Clinical Chemistry	X*			X	X		X	X	X	X	X	X	X			
Urine Dipstick Testing (or Urinalysis)	X*	X		X	X	X	X	X	X	X	X	X				* Perform within 7 days before first dose. After C1, collect samples within 3 days before D1 of each cycle. Urine dipstick testing for participants with proteinuria ≥2+ should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ or negative for 2 consecutive treatment cycles If lenvatinib is discontinued, urine dipstick testing is no longer required. After Screening, urine dipstick-testing for protein will be performed within 3 days before Day 1 of every cycle while participants are taking lenvatinib.
Urinalysis	X*									X		X	X			Perform within 7 days before first dose. During study intervention, obtain urinalysis at every 6th cycle (eg, 6, 12, 18, etc.), within 3 days of dosing. * Assessment should be done within 7 days of C1D1.

Study Period	Crossover Screening	Intervention (21-Day Cycles)											Post-Intervention Visit			Notes
Visit/Cycle Number		C1			C2		C3	C4	C5	C6 to C35	≥C36	EOT	Safety FU	Efficacy FU	Survival FU	
Cycle Day		1	8	15	1	15	1	1	1	1	1					
INR or PT and aPTT or PTT	X*															* Perform within 7 days prior to the first dose. Additional testing is to be performed as clinically indicated for participants taking anticoagulants.
T3 or FT3, T4, TSH	X*				X			X		X	X		X			* Perform screening labs within 7 days prior to the first dose, then at C2 and every 2 cycles thereafter (C4, C6, C8, etc.). Participants may be dosed in subsequent cycles after C1D1 while thyroid function test are pending. Free T3/T4 is acceptable if total T3/T4 cannot be determined. The central laboratory may be used only if the local laboratory cannot perform these tests.
Pharmacokinetics/Pharmacodynamics/ Biomarkers (Central Laboratory)																
Serum for Pembrolizumab PK		X			X					X*						Collect predose on C1D1, C2D1, and *C8D1.
Serum Anti-pembrolizumab Antibodies (ADA)		X			X					X*						Collect predose on C1D1, C2D1, and *C8D1.

Study Period	Crossover Screening	Intervention (21-Day Cycles)											Post-Intervention Visit			Notes
Visit/Cycle Number		C1			C2		C3	C4	C5	C6 to C35	≥C36	EOT	Safety FU	Efficacy FU	Survival FU	
Cycle Day		1	8	15	1	15	1	1	1	1	1					
Plasma for Lenvatinib PK		X		X	X											C1D1: postdose at any time from 0.5 to 4h; collection from 6 to 10h postdose is optional. C1D15: collect predose within 2h of lenvatinib dosing and postdose at any time from 2 to 12h postdose. C2D1: collect predose within 2h of lenvatinib dosing and postdose at any time from 0.5 to 4h; collection from 6 to 10h postdose is optional. Postdose samples will not be collected if lenvatinib dosing is on hold due to dose modifications, etc.
Blood for Plasma Biomarkers		X			X		X		X	X	X	X				Collect at predose on D1 of C1, C2, C3, C5, C7, C9, C11, C13, C15, C17, then on D1 of every 3 cycles until EOT, including at the EOT visit.
Blood for Serum Biomarkers		X		X	X		X		X			X				Collect predose. Collect on C1D1, C1D15, C2D1, C3D1, C5D1, and at EOT.
Blood for RNA Analysis		X			X		X		X			X				Collect predose on C1D1, C2D1, C3D1, C5D1, and at EOT.
Blood for Circulating Tumor Nucleic Acids		X			X		X		X	X	X	X				Collect at predose on D1 of C1, C2, C3, C5, C7, C9, C11, C13, C15, C17, then on D1 of every 3 cycles until EOT, including at the EOT visit.

Study Period	Crossover Screening	Intervention (21-Day Cycles)											Post-Intervention Visit			Notes
Visit/Cycle Number		C1			C2		C3	C4	C5	C6 to C35	≥C36	EOT	Safety FU	Efficacy FU	Survival FU	
Cycle Day		1	8	15	1	15	1	1	1	1	1					
Patient reported Outcomes (PRO)*																
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. * Obtain on Day 1 of every cycle from C1 through C9, then Day 1 of every other cycle through C17 (C9, C11, C13, C15, C17), then collect every 3 cycles through C35 (C20, C23, C26, C29, C32, C35). Obtain at EOT and Safety FU. Refer to 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*			

Abbreviations: ADA = anti-drug antibodies (pembrolizumab); AE = adverse event; aPTT = activated partial thromboplastin time; BP = blood pressure; β-HCG; = β human chorionic gonadotropin; C = cycle; CBC = complete blood count; CXDY= Cycle X Day Y; d = days; D = day; D/C = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; EOT = end of treatment; ePRO = electronic patient reported outcome; EQ-5D-5L = European Quality of Life Five-Dimensional Five-Level Scale Questionnaire; FSH = follicle-stimulating hormone; FT3 = free triiodothyronine; FU = follow-up; h = hours; INR = international normalized ratio; PD = progressive disease; PK = pharmacokinetics; PRO = patient reported outcome; PT = prothrombin time; PTT = partial 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; SAE = serious adverse event; SoA = schedule of activities; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WOCBP = women of childbearing potential; WONCBP = women of non-childbearing potential; Y = year.

1.3.4 Second Course

NOTE: As of Amendment 07, there will be no Second Course. This section is no longer applicable.

2 INTRODUCTION

Lenvatinib with or without pembrolizumab and SOC chemotherapy study interventions are being evaluated for previously treated participants with R/M HNSCC who progressed after platinum-containing chemotherapy at any time (with or without cetuximab) and a PD-1/PD-L1 inhibitor, in this randomized, open-label, Phase 2 study.

2.1 Study Rationale

Head and neck cancer describe an anatomically heterogeneous group of cancers that arise most often from the oral cavity, the oropharynx, 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]. As the sixth most common cancer worldwide, head and neck cancer is diagnosed in approximately 630,000 new patients annually, accounting for 350,000 deaths every year. [Vigneswaran, N. 2014]. Head and neck cancers have 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 patients 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 patients with Stage I and II disease. However, despite intensive multimodal treatment, approximately 50-60% of patients with locally advanced Stage III or Stage IV HNSCC recur initially with locoregional disease. However, a significant proportion of these patients ultimately have incurable disease recurrence requiring palliative systemic treatment. The prognosis for patients with R/M HNSCC is dismal and OS is less than 1 year [Argiris, A., et al 2017].

Patients 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. Patients who are asymptomatic usually are treated with monotherapy to balance the side-effects associated with combination regimens. Options for first-line 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 demonstrated 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 to 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) in first-line treatment 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 regardless of PD-L1 expression status, there was a clinically meaningful difference in OS when comparing pembrolizumab plus chemotherapy with standard treatment. The pembrolizumab plus chemotherapy group had a longer duration of response than the EXTREME regimen and the safety profile was

comparable. There was a clinically meaningful difference in OS when comparing pembrolizumab monotherapy group compared to standard treatment for participants whose tumors expressed PD-L1 (CPS ≥1). The pembrolizumab monotherapy group had more responders who achieved a CR and a more durable duration of response (DOR). The safety profile for pembrolizumab monotherapy was favorable. Based on this data, pembrolizumab is now approved in the US, Japan, Western Europe and other countries as monotherapy and in combination with chemotherapy for 1L HNSCC treatment.

After failure of first-line therapy in the R/M setting, objective responses to second-line cytotoxic chemotherapy are uncommon, particularly when contemporary response criteria are applied. Single-agent therapy and combination regimens using either conventional cytotoxic chemotherapy and/or molecularly targeted agents, combined with best supportive care is palliative for patients with R/M HNSCC, and their prognosis is generally poor despite these therapies [National Comprehensive Cancer Network 2018]. The most widely used agents include platinum compounds (cisplatin, carboplatin), taxanes (docetaxel, paclitaxel), 5- FU, and single-agent cetuximab. Other single agents have produced higher response rates but these have generally been associated with increased toxicity, and without an impact on OS [Vermorken, J. B. 2010] [Price, K. A. 2012] [Colevas, A. D. 2006] [Sacco, A. G. 2015] [Dorsey, K. 2013]. Furthermore, there is no approved therapy or supporting data from existing clinical trials for the treatment of patients who progress after failure of prior immunotherapy (PD-1/PD-L1 inhibitors, such as nivolumab and pembrolizumab).

In preclinical models, lenvatinib decreased the 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 [Kato, Y., et al 2019]. 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.

The ongoing lenvatinib + pembrolizumab 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 demonstrated an initial ORR of 40.9% that strongly suggest greater efficacy with the combination of lenvatinib + pembrolizumab than with either single agent, a possibly additive effect. Follow-up data for the KEYNOTE-146 HNSCC cohort demonstrated an overall ORR of 46% (10/22; 95% CI: 24.4, 67.8). The median DOR was 8.2 months (95% CI: 2.2, 12.6), and the median progression-free survival (PFS) was 4.7 months (95% CI: 4.0, 9.8). In total, treatment was ongoing for 14% (3/22) of patients with HNSCC at the time of data cutoff [Taylor, M. H., et al 2020].

Given the approvals of pembrolizumab and nivolumab for patients with R/M HNSCC who have progressed on prior platinum therapy as well as approval for pembrolizumab for patients with 1st line R/M HNSCC, there is a growing medical need for safe and efficacious subsequent treatment options for patients who experience disease progression on or after immunotherapy treatment.

Data suggest that the combination or sequencing of immune checkpoint inhibitors may be used to restore activity in participants who have progressed on a particular inhibitor. This strategy may also offer a more powerful tool to induce immune activity in tumors that respond poorly (ie, those that may have a greater level of immune suppression) [Pennock, G. K. 2015]. Additionally, combining therapies with differing mechanisms of action has the potential to further enhance their clinical benefits compared with using single-agent immunotherapy.

The intended population of this Phase 2 study represents patients with a high unmet medical need considering all of these patients have incurable R/M HNSCC disease. In these patients who have failed prior platinum-containing therapy and have acquired resistance to immunotherapy, the combination of pembrolizumab with lenvatinib could lead to a greater depth of response and an increase in OS. The current study is designed to further evaluate the safety and efficacy of combination therapy with pembrolizumab + lenvatinib as 2L+ treatment for R/M HNSCC patients.

2.2 Background

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

Lenvatinib inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib inhibits other kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; platelet-derived growth factor receptor alpha (PDGFRα), KIT, and RET. Lenvatinib also exhibited antiproliferative activity in cell lines dependent on activated FGFR signaling with a concurrent inhibition of FGF-receptor substrate 2α phosphorylation. Refer to the respective IBs/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 upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald, R. J., et al 2005] [Okazaki, T., et al 2001].

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

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

R/M disease (KN012, KN055, KN040, and KN048), as well as planned studies, LEAP-009 and 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. Pembrolizumab + lenvatinib study 111/KEYNOTE-146 is summarized under ongoing clinical studies of pembrolizumab in HNSCC. Refer to the respective IBs/approved labeling for full lists of ongoing studies and detailed background information on pembrolizumab and lenvatinib.

Ongoing Clinical Studies of Pembrolizumab in HNSCC

KEYNOTE-012 (KN012)

KN012 is a Phase 1b, multi-cohort 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. 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 R/M 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 R/M HNSCC population (n=192), the ORR was 21.9% (95% CI; 12.5%, 34.0%) in HPV positive participants and 15.9% (95% CI: 10.0%, 23.4%) in HPV-negative participants. In a separate publication, when PD-L1 expression analyses were restricted to only tumor cells (TPS), there was no statistically significant increase ORR with PD-L1 positive (≥1%) versus negative (<1%) tumors. Conversely, when PD-L1 expression was assessed both on tumor cells and immune cells by evaluating the CPS, PD-L1 expression significantly correlated with ORR, PFS, and OS [Chow, L. Q., et al 2016]. The ORR with pembrolizumab is greater than that of existing standard single-agent cytotoxic chemotherapies such as cetuximab, which in the setting of second-line R/M disease has an ORR of approximately 11% based on a meta-analysis estimating a pooled ORR for cetuximab based on 3 Phase II trials in the R/M HNSCC setting. Median OS was 8.5 months (95% CI: 6.5, 10.5), compared to the historical OS rate of 6 months for participants who progress following first-line treatment. The 6-month PFS rate was 24.9% [Lala, M., et al 2018].

Importantly, the responses seen with pembrolizumab were durable. Among participants with R/M HNSCC, the DOR ranged from 1.8+ to 21.8+ months, and the median was not reached. Among participants who responded (n=34), 85% of responses lasted ≥6 months and 71% of responses lasted ≥12 months, and 65% of responses were ongoing at the data cutoff with 3 lasting at least 2 years [Soulieres, D., et al 2017]. These results demonstrate the consistent durability of responses seen with pembrolizumab treatment and compare favorably to SOC

chemotherapy or epidermal growth factor receptor inhibitors, which have reported median DOR of 4 to 6 months.

These results of KN012 demonstrate consistent and clinically meaningful activity of pembrolizumab in heavily pretreated participants with HNSCC and demonstrate a robust and unprecedented antitumor activity observed compared to 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 R/M 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%, 23%) with a median DOR of 8 months (range, 2+ to 12+ months); the stable disease rate was 19% (n=33; 95% CI: 14%, 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 R/M 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 prior to 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 to 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 patients in the pembrolizumab group and 207 (83%) of 248 patients in the SOC group had died. The median OS in the intention-to-treat (ITT) population was 8.4 months (95% CI 6.4-9.4) with pembrolizumab and 6.9 months (5.9-8.0) with SOC (hazard ratio 0.8, 0.65-0.98; 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 CPS1 tumor score, the HR for OS was 0.74 (95% CI 0.58-0.93; nominal p=0.0049), with a median survival of 8.7 months (95% CI 6.9-11.4) for pembrolizumab vs. 7.1 months (5.7-8.3) with SOC. In participants whose tumor had PD-L1 TPS ≥50% expression, the HR for death was 0.53 (95% CI 0.35-0.81; nominal p=0.0014), and median OS was 11.6 months (95% CI 8.3-19.5) compared to 6.6 months (4.8-9.2) for pembrolizumab and SOC, respectively.

Fewer patients treated with pembrolizumab than with SOC had treatment-related AEs (63% vs. 84%), as well as higher toxicity adverse events (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-fluorouracil chemotherapies versus platinum plus 5-fluorouracil plus cetuximab (EXTREME regimen) in participants with first-line R/M HNSCC. A total of 882 participants with first-line 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). Randomization was stratified by PD-L1 tumor expression (strongly positive TPS ≥50% vs. not strongly positive), HPV status for oropharyngeal cancer (positive vs. negative), and ECOG performance status (0 vs. 1). The primary endpoints of the study are PFS per RECIST 1.1 as assessed by BICR, and OS. Enrollment is closed, but participants are ongoing in the study.

Data from the second interim analysis were presented at the 2018 European Society of Medical Oncology (ESMO) 2018 for KEYNOTE-048[Burtness, B., et al 2018]. For OS, pembrolizumab monotherapy was superior to the EXTREME regimen in participants with a combined positive score (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 0.64-0.96, p=0.0086) and a median OS of 12 months versus 10.3 months in participants receiving the EXTREME regimen.

Confirmed ORR for pembrolizumab versus EXTREME was 23% vs. 36% for CPS ≥20 with a more durable DOR of 20.9 vs. 4.2 months, and 19% vs. 35% for CPS ≥1 with a median DOR of 20.9 versus 4.5 months for CPS ≥1.

Pembrolizumab monotherapy had a more favorable toxicity profile compared to the EXTREME regimen with few related AEs (58.3% vs. 96.9%), fewer related Grade 3-5 AEs (16.7% vs. 69%), and fewer related AEs that led to treatment discontinuation (4.7% vs. 19.9%).

At final analysis, for 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 HR of 0.74 [95% CI: 0.61, 0.90] for CPS ≥1 and HR of 0.58 [95% CI: 0.44, 0.78] for CPS ≥20. In the population of all participants, there was a clinically meaningful difference in OS when comparing pembrolizumab monotherapy with standard treatment. The pembrolizumab monotherapy group had more responders who achieved a CR and a more durable DOR (22.6 vs. 4.5 months). The safety results at 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=0.0034, median 13 vs. 10 months). Additionally, the safety profiles for pembrolizumab + chemotherapy and the EXTREME regimen were comparable (95.3% vs. 96.9% related AEs for pembrolizumab vs. EXTREME; 71.0% vs. 69.0% related Grade 3-5 AEs for pembrolizumab vs. EXTREME; and 22.8% vs. 19.9% related AEs that led to treatment discontinuation). At final analysis, pembrolizumab + chemotherapy OS results (HR 0.72 [95% CI: 0.60, 0.87]) 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). 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 vs. 4.3 months for CPS ≥1 and 7.1 vs. 4.2 months for CPS ≥20. The safety results at final analysis were similar to those observed at the second interim analysis.

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 iRECIST. 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, 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 TRAEs occurred in 72.7% of participants [Grade 3 TRAEs 15 (68.2%) and Grade 4 TRAEs 1 (4.5%)]. The most common TRAEs 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 TRAEs 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].

Follow-up data for the KEYNOTE-146 HNSCC cohort demonstrated an overall ORR of 46% (10/22; 95% CI: 24.4, 67.8). The median DOR was 8.2 months (95% CI: 2.2, 12.6), and the median PFS was 4.7 months (95% CI: 4.0, 9.8). In total, treatment was ongoing for 14% (3/22) of patients with HNSCC at the time of data cutoff [Taylor, M. H., et al 2020].

Overall, the study demonstrated 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, and melanoma 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]. 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 2 study.

LEAP-010

LEAP-010 is an ongoing Phase 3, randomized, double-blind, placebo-controlled study comparing pembrolizumab monotherapy versus pembrolizumab in combination with lenvatinib for patients with 1st line R/M HNSCC. Primary outcome measures include ORR per RECIST 1.1, PFS per RECIST 1.1, and OS. The study enrolled a total of 511 patients. To date, both IA1 and IA2 have been completed. ORR at IA1 was significantly higher for the lenvatinib + pembrolizumab arm at 46.1% compared with 25.4% for the pembrolizumab plus placebo arm (difference 20.2%, 95% CI 10.5-29.6, P=0.0000251). Median PFS at IA1 was statistically higher at 6.2 months for the lenvatinib + pembrolizumab arm versus 2.8 months for the pembrolizumab plus placebo arm (HR 0.64, 95% CI 0.50-0.81; P=0.0001040) [Licitra, L., et al 2024]. Median OS at IA2 was found not to be statistically different between treatment arms. Median OS was 15.0 months for the lenvatinib + pembrolizumab arm versus 17.9 months for the pembrolizumab plus placebo arm (HR 1.15, 95% CI: 0.91-1.45; P=0.882). The study did not proceed with additional protocol specified efficacy analyses, because the probability of reaching statistical significance for OS was low [Merck & Co., Inc. 2023]. Therefore, LEAP-010 did not meet its primary endpoint of OS, despite demonstrating a statistically significant ORR and PFS with lenvatinib plus pembrolizumab compared with those of pembrolizumab plus placebo. In addition, the safety profile was consistent with previously reported data; more TRAEs were found in participants receiving lenvatinib + pembrolizumab.

2.3 Benefit/Risk Assessment

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

With the approval of immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway as a second-line therapy for HNSCC, there is an unmet medical need for safe and efficacious therapy in participants whose disease has progressed with this treatment. SOC chemotherapy will be utilized in the control arm. 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 lenvatinib + pembrolizumab a promising second-line or greater therapeutic option in participants with R/M HNSCC, regardless of PD-L1 expression.

Refer to the informed consent documents and the respective IBs/approved labeling for additional details regarding specific benefits and risks for participants participating in this clinical study, and detailed background information on pembrolizumab and lenvatinib.

NOTE: Based on the results of a periodic review of safety data (data cutoff 31-MAY-2024) for LEAP-009, the study will be discontinued. At the request of the eDMC, OS data were provided for review, though there was no preplanned statistical analysis for OS. At this safety analysis, the OS Kaplan-Meier curves did not favor the combination of lenvatinib + pembrolizumab versus SOC chemotherapy. Furthermore, it was considered that additional follow-up OS outcomes in favor of the combination are unlikely to support a clinically meaningful favorable benefit-risk ratio. The prespecified interim and final analyses of the study described in Section 9 will not be performed. Selected analyses of safety endpoints will be performed at the end of the study; there will be no further analyses of efficacy or ePRO endpoints.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

Males and females with R/M HNSCC, who are at least 18 years old, and who have progressed after platinum-containing chemotherapy at any time (with or without cetuximab) and a PD 1/PD-L1 inhibitor will be enrolled in this study.

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

NOTE: Based on a periodic review of safety data (data cutoff 31-MAY-2024) for LEAP-009, OS Kaplan-Meier curves did not favor pembrolizumab + lenvatinib versus SOC chemotherapy, and it was considered that additional follow-up OS outcomes in favor of the combination are unlikely to support a clinically meaningful favorable benefit-risk ratio. The prespecified interim and final analyses of the study described in Section 9 will not be performed. Selected analyses of safety endpoints will be performed at the end of the study; there will be no further planned analyses for efficacy and ePRO endpoints. Updated analyses are described in Section 9.

In alignment with the study-specific investigator letter dated 05-SEP-2024, all participants should discontinue the combination of lenvatinib + pembrolizumab (Arm 1) or lenvatinib monotherapy (Arm 3), as applicable. On a case-by-case basis, investigators may contact the Sponsor for consideration of continuing lenvatinib plus pemrolizumab or lenvatinib monotherapy if they assess the participant is deriving clinical benefit. Treatment with SOC chemotherapy (Arm 2) can continue at the discretion of the investigator until a protocol specified discontinuation criterion is met. Participants who are continuing study treatment should follow the modified protocol study procedures as specified in this amendment.

All participants beyond the 30-day Safety Follow-up Visit in the initial treatment or Crossover treatment phases should be discontinued from the study; however, standard safety reporting should continue, as applicable. As of Amendment 07, 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 required to be submitted to the iCRO; however, tumor imaging with investigator assessment should continue per protocol. Biomarker specimen collection is discontinued. The 30-day Safety Follow-up Visit is the last required visit.

Primary Objective	**Primary Endpoint**
Objective: to compare lenvatinib + pembrolizumab combination therapy and SOC chemotherapy with respect to OS. Hypothesis (H1): lenvatinib + pembrolizumab is superior to SOC with respect to OS.	OS: The time from randomization to death due to any cause.
Secondary Objectives	**Secondary Endpoints**
Objective: to compare lenvatinib + pembrolizumab combination therapy and SOC chemotherapy with respect to PFS per RECIST 1.1 by BICR Hypothesis (H2): lenvatinib + pembrolizumab is superior to SOC with respect to PFS per RECIST 1.1 by BICR.	PFS: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.
Objective: to compare lenvatinib + pembrolizumab combination therapy and SOC chemotherapy with respect to ORR per RECIST 1.1 as assessed by BICR. Hypothesis (H3): lenvatinib + pembrolizumab is superior to SOC with respect to ORR per RECIST 1.1 by BICR.	Objective Response (OR): complete response (CR) or partial response (PR).
Objective: to assess the efficacy of lenvatinib + pembrolizumab combination therapy and SOC chemotherapy with respect to DOR per RECIST 1.1, by BICR.	DOR: 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 lenvatinib + pembrolizumab combination therapy, SOC chemotherapy, and lenvatinib monotherapy	-AEs -Study drug discontinuations due to AEs

Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
Objective: to assess the efficacy of lenvatinib monotherapy with respect to ORR, PFS, DOR per RECIST 1.1 by BICR, and OS.	-OR -PFS -DOR -OS
Objective: to evaluate changes from baseline in HRQoL with lenvatinib + pembrolizumab combination therapy, SOC chemotherapy and lenvatinib monotherapy using the EORTC QLQ-C30 and EORTC QLQ-H&N35.	Scores from the EORTC QLQ-C30 and 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 health status with lenvatinib + pembrolizumab combination therapy, SOC chemotherapy and lenvatinib monotherapy 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, including HPV status, 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.
Objective: to assess the PK of lenvatinib monotherapy and when co-administered with pembrolizumab.	Plasma concentration of lenvatinib versus time.

4 STUDY DESIGN

4.1 Overall Design

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

NOTE: Based on a periodic review of safety data (data cutoff 31-MAY-2024) for LEAP-009, OS Kaplan-Meier curves did not favor pembrolizumab + lenvatinib versus SOC chemotherapy, and it was considered that additional follow-up OS outcomes in favor of the combination are unlikely to support a clinically meaningful favorable benefit-risk ratio. The prespecified interim and final analyses of the study described in Section 9 will not be performed. Selected analyses of safety endpoint will be performed at the end of the study; there will be no further planned analyses for efficacy and ePRO endpoints. Updated analyses are described in Section 9.

In alignment with the study-specific investigator letter dated 05-SEP-2024, all participants should discontinue the combination of lenvatinib + pembrolizumab or lenvatinib monotherapy, as applicable. On a case-by-case basis, investigators may contact the Sponsor for consideration of continuing lenvatinib plus pemrolizumab or lenvatinib monotherapy if they assess the participant is deriving clinical benefit. Treatment with SOC chemotherapy (Arm 2) can continue at the discretion of the investigator until a protocol specified discontinuation criterion is met. Participants who are continuing study treatment should follow the modified protocol study procedures as specified in this amendment.

All participants beyond the 30-day Safety Follow-up Visit in the initial treatment or Crossover treatment phases should be discontinued from the study; however, standard safety reporting should continue, as applicable. As of Amendment 07, 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 required to be submitted to the iCRO; however, tumor imaging with investigator assessment should continue per protocol. Biomarker specimen collection is discontinued. The 30-day Safety Follow-up Visit is the last required visit.

This is a Phase 2, randomized, open-label, multicenter, study of lenvatinib + pembrolizumab, SOC chemotherapy and lenvatinib monotherapy. Participants with R/M HNSCC who have progressed after platinum chemotherapy at any time (with or without cetuximab) and after treatment with immunotherapy (PD-1/PD-L1 inhibitors) will be enrolled in this study. This study will be conducted in participants with measurable disease, per RECIST 1.1 by BICR, regardless of PD-L1 status.

The site’s study team must have reviewed and submitted pre-study images that are of diagnostic quality from at least 2 dates to determine that radiographic progression has occurred per RECIST 1.1 following initiation of the PD-1/PD-L1 inhibitor. These images include at a minimum, the baseline image for prior anti-PD-1/PD-L1 or an image showing nadir during prior anti-PD-1/PD-L1 treatment and an image showing progression on prior anti-PD-1/PD-L1 treatment (within 12 weeks of last doses of anti-PD-1/PD-L1 treatment). These pre-study images will be submitted to the iCRO to verify that the images are of

diagnostic quality prior to randomization (see Section 8.2.1.1). The baseline tumor image collected during the Screening period must be also submitted to the iCRO for verification of measurable disease per RECIST 1.1 for eligibility prior to randomization.

Note: The pre-study scan demonstrating progression on prior PD-1/PD-L1 treatment can be used as screening tumor imaging for the study if it is performed within 28 days before the date of randomization and can be assessed by the iCRO.

An archival or newly obtained (within 90 days prior to start of study treatment) tumor specimen for PD-L1 biomarker analysis will be required prior to randomization.

Participants will be stratified prior to randomization according to ECOG PS and PD-L1 status (see Section 6.3.2).

Initial Treatment

Eligible participants will be centrally randomized to receive lenvatinib + pembrolizumab (Arm 1), SOC chemotherapy (Arm 2) or lenvatinib monotherapy (Arm 3).

- Lenvatinib + pembrolizumab combination therapy (Arm 1), in which participants will be enrolled and treated with the combination of pembrolizumab (200 mg 30-minute IV infusion Q3W) for 35 cycles + lenvatinib (20 mg PO QD) until centrally verified PD, or until a discontinuation criterion is met.

- SOC chemotherapy (Arm 2), in which participants will be enrolled and treated with investigator's choice of SOC chemotherapy (docetaxel, paclitaxel, cetuximab, or capecitabine) until centrally verified disease progression or a discontinuation criterion is met.

- Lenvatinib monotherapy (Arm 3), in which participants will receive lenvatinib monotherapy (24 mg orally PO, QD) until centrally verified disease progression or a discontinuation criterion is met.

The study design is shown in Figure 1 (Initial Treatment).

A single-arm futility analysis (Figure 1) for the lenvatinib monotherapy arm will be conducted after 30 participants have been randomized to lenvatinib monotherapy (Arm 3) and have been followed up for approximately 12 weeks after study entry. Randomization to this arm will be paused after the 30th participant is randomized. If the number of responses by BICR is ≥3, randomization to the lenvatinib monotherapy arm will be resumed such that a total of N=100 participants will be enrolled in this arm. If the number of responses is ≤2, randomization to the lenvatinib monotherapy arm will be permanently stopped. If the number of responses by BICR ≥3 is observed prior to the 30th participant, the randomization to the lenvatinib monotherapy arm will not be paused.

Overall, approximately 400 participants will be randomized, with approximately 100 participants randomized to the lenvatinib arm and 150 participants to each of the SOC

chemotherapy and lenvatinib + pembrolizumab treatment arms. Enrollment was completed on 05-SEP-2024.

Participants will be evaluated with radiographic imaging to assess response to study intervention every 6 weeks from the date of randomization. After 1 year (48 weeks), imaging will occur every 9 weeks until centrally verified PD or initiation of a new anticancer regimen. Schedule should be followed regardless of treatment delays. All imaging obtained during the study will be submitted to the iCRO for BICR, which will assess the images using RECIST 1.1 (Section 4.2.1.1.1) for determination of ORR and PFS. The tumor imaging showing site-assessed PD should be submitted immediately for verification by BICR. Treatment beyond centrally verified radiographic PD per RECIST 1.1 may be permitted at the discretion of the investigator after consultation with the Sponsor and obtaining documented informed consent.

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

AE monitoring will be ongoing throughout the study. AEs will be graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) CTCAE, version 5.0.

Participants in the lenvatinib + pembrolizumab combination arm may continue receiving pembrolizumab for up to 35 cycles (approximately 2 years), until centrally verified PD, or until a discontinuation criterion is met. Participants may continue to receive lenvatinib monotherapy until disease progression or unacceptable toxicity. Either pembrolizumab or lenvatinib may be interrupted or discontinued due to toxicity and the participant may continue in the study receiving the remaining study treatment intervention.

Participants receiving lenvatinib monotherapy may add pembrolizumab to lenvatinib upon centrally verified PD by RECIST 1.1 with Sponsor consultation. As per Section 4.3.2, lenvatinib monotherapy dose (24 mg) should be decreased to 20 mg daily or at the last dose level when given in combination with pembrolizumab. Treatment with SOC chemotherapy may continue until a discontinuation criterion (see Section 7.1) is met. Participants receiving SOC chemotherapy may start pembrolizumab and lenvatinib upon centrally verified radiographic PD by RECIST 1.1 with Sponsor consultation. As of Amendment 07, participants in the SOC chemotherapy arm or lenvatinib monotherapy arm may not crossover to receive lenvatinib + pembrolizumab at the time of disease progression.

All decisions to continue intervention beyond centrally verified radiographic PD by RECIST 1.1 require consultation with the Sponsor.

Crossover Treatment

Participants who experience centrally verified PD in the lenvatinib monotherapy or SOC chemotherapy arms can cross over to receive lenvatinib + pembrolizumab at time of disease progression with Sponsor consultation. All screening evaluations must be completed and reviewed to confirm potential participants meet all treatment eligibility criteria. For participants who were randomized initially to lenvatinib monotherapy, lenvatinib treatment

may be continued during Crossover screening at the discretion of the investigator after consultation with the Sponsor and if the study is ongoing. As of Amendment 07, participants in the SOC chemotherapy arm or lenvatinib monotherapy arm may not crossover to receive lenvatinib + pembrolizumab at the time of disease progression.

Second Course Treatment

NOTE: As of Amendment 07, there will be no Second Course Treatment. This section is no longer applicable.

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

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

4.2 Scientific Rationale for Study Design

This is an open-label, randomized study with 3 treatment arms to assess the safety and efficacy of lenvatinib + pembrolizumab, SOC chemotherapy and lenvatinib monotherapy in participants with R/M HNSCC who progressed after platinum-containing chemotherapy at any time (with or without cetuximab) and a PD-1/PD-L1 inhibitor. The study is open label because of the different infusion times needed for Arms 1 and 2.

In order to provide a direct comparison of OS between the lenvatinib + pembrolizumab arm and SOC chemotherapy arm, 150 participants will be enrolled in each of these arms. As lenvatinib monotherapy has not been studied in patients with R/M HNSCC patient population, a lenvatinib monotherapy arm has been included to provide an estimation of the safety and efficacy of this treatment in this patient population. In order to accomplish this, the sample size for this arm will be 100 participants with interim futility analysis to be conducted for this lenvatinib monotherapy arm. The preliminary results detailed in Section 2.2.3, for an open-label, Phase 1b/2 study (Study E7080-A001-111 [Study 111/KN-146]) to assess the safety and preliminary antitumor activity of the combination of lenvatinib + pembrolizumab in participants with selected solid tumors including R/M HNSCC demonstrated promising clinical activity, supporting further evaluation of the combination of lenvatinib + pembrolizumab in participants with R/M HNSCC [Taylor, M. H., et al 2018a].

Given the lack of treatment options and high unmet medical need for patients with R/M HNSCC who progress on immune checkpoint inhibitor therapy, the safety and efficacy of lenvatinib + pembrolizumab will be assessed in this patient population. If the safety profile is acceptable and this combination improves OS compared to SOC chemotherapy, this study could support the regulatory approval of the combination of lenvatinib + pembrolizumab in participants with R/M HNSCC who progress after treatment with an anti-PD-1/PD-L1 mAb.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

Primary Efficacy Endpoint

This study will use OS as the primary endpoint. OS has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies. In addition, this change in primary endpoint is based on the updated statistical assumptions secondary to emerging external data for this patient population.

Secondary Efficacy Endpoints

PFS is an acceptable measure of clinical benefit for a late stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The use of BICR and RECIST 1.1, to assess PFS is typically considered acceptable by regulatory authorities. 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.

OR based on RECIST 1.1 as assessed by BICR will serve as an additional efficacy endpoint. The use of BICR and RECIST 1.1 to assess OR is typically considered acceptable by regulatory authorities. Images will be submitted to an iCRO and read by an independent central reviewer blinded to treatment assignment to minimize bias in the response assessments.

DOR per RECIST 1.1 assessed by BICR will serve as an additional measure of efficacy and is a commonly accepted endpoint by both regulatory authorities and the oncology community.

4.2.1.1.1 RECIST 1.1

RECIST 1.1 will be used by BICR when assessing images for efficacy measures. Although traditional RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented an adjustment to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ. Refer to Section 8.2.1.7 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 EuroQoL-5D-5L (EQ-5D-5L) PRO instrument.

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 health-related quality of life 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 their 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].

4.2.1.3.2 Pharmacokinetic Endpoints

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

4.2.1.3.3 Rationale for Anti-drug Antibody (ADA) Assessment

To evaluate the immunogenicity and exposure of pembrolizumab in this indication, sample collections for analysis of ADA may be performed in participants receiving lenvatinib + pembrolizumab (Arm 1). Sampling may be reduced or discontinued upon alignment with health authorities.

4.2.1.3.4 Pharmacodynamic Endpoints

No pharmacodynamic endpoints are planned for this study.

4.2.1.3.5 Planned Exploratory Biomarker Research

Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies, including novel 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- or and growth factor related signaling pathways related to pembrolizumab and lenvatinib may also be explored. Thus, genome-wide approaches may be used for this effort. Note that in order to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Circulating tumor DNA and/or RNA may also be evaluated from blood samples.

Tumor and blood RNA analyses

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

Proteomics and immunohistochemistry (IHC) using blood or tumor

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

Other blood-derived biomarkers

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

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

4.2.2 Rationale for Selected Standard-of-care Chemotherapies

The proposed choice of docetaxel, paclitaxel, cetuximab, or capecitabine as single-agent, SOC chemotherapy is based on the NCCN guidelines for R/M HNSCC recognizing these agents as appropriate treatment options in the second-line setting, input from key opinion leaders, and prior precedence in 2L registration trials**.**

Docetaxel

Docetaxel has a registered indication in squamous cell carcinoma of the head and neck for locally advanced disease in combination with cisplatin and 5-fluorouracil. However, it is commonly given in the R/M setting as a single agent with RR ranging from 6-42%, depending on the line of therapy and patient population. For example, significant clinical activity of weekly docetaxel in a Phase 2 study of 38 patients was seen with a response rate of 42% in the 1L R/M setting [Hitt, R., et al 2006]. In addition, a randomized Phase 2 study of weekly docetaxel versus methotrexate showed a higher response rate for docetaxel (27%) in the 1L R/M setting, although survival rates were comparable [Guardiola, E., et al 2004]. Phase 3 studies using weekly docetaxel as the control arm in the 1L/2L setting have also been performed, confirming the activity of docetaxel in the predominantly 2L setting, although RRs were more modest at 6.2% [Argiris, A., et al 2013]. Thus, single-agent docetaxel on a weekly schedule has been shown to have activity in R/M disease and is utilized particularly in head and neck cancer patients who have not been previously exposed to taxanes.

Paclitaxel

Paclitaxel has been shown in several clinical trials to demonstrate clinical efficacy for the treatment of R/M HNSCC. The majority of these studies are in mixed populations of 1L and 2L R/M HNSCC. In the BERIL-1 study, paclitaxel plus buparlisib was compared versus paclitaxel plus placebo for patients with second-line R/M HNSCC. Approximately 78 participants with second-line R/M HNSCC were enrolled in this trial and received paclitaxel 80 $^{mg/m2}$ weekly. ORR was observed to be 14% for the paclitaxel plus placebo arm. For this treatment arm, median OS was 6.5 months (5.3-8.8) and median PFS was 3.5 months (2.2-3.7) [U.S. Prescribing Information 2017].

Cetuximab

Cetuximab has a registered indication for the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy. In an open-label Phase 2 study of 103 R/M head and neck cancer patients treated with single-agent cetuximab after failing to respond to platinum-based therapy, the response rate was 13% [Vermorken, J. B., et al 2007]. The activity of single-agent cetuximab in R/M disease has also been seen in other studies, with response rates of 8-11% [Fury, M. G., et al 2012].

Capecitabine

Capecitabine is an active, feasible and well-tolerated mode of palliative treatment for advanced head and neck cancer patients who have previously received platinum-based chemotherapy. In an open-label Phase 2 study of 40 R/M head and neck cancer patients (33 patients were evaluable for assessment of response) treated with single-agent capecitabine after failing to respond to platinum-based therapy, the ORR was 24.2%. These patients had documented PD on previous platinum-based therapy in the R/M setting (15%) or received platinum-based therapy in the local setting with no documentation of progression (85%). 17.5% of the patients included in this study could be considered as having primary locoregional disease only, and outcomes were not reported separately for the R/M patients. The activity of single-agent capecitabine in combination with radiotherapy and/or CT in advanced or R/M disease has also been seen in other studies, with response rates of 23.5% to 68% [Martinez-Trufero, J., et al 2010].

For participants randomized to the SOC chemotherapy arm, the investigator will be allowed to select one of the 4 options above that has not been previously administered to the participant. When choosing an SOC chemotherapy, the investigator should refer to the respective approved product label (with special consideration for any contraindications, special warnings and precautions of use), and/or according to local guidelines.

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 pembrolizumab 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 pembrolizumab 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 OS at 200 mg Q3W across multiple indications

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

4.3.2 Lenvatinib

Monotherapy:

Modeling of PK data in Studies E7080-E044-101 (25 mg QD) and E7080-A001-102 (10 mg BID) demonstrated that PFS and PR and SD significantly increased with higher lenvatinib exposure (based on C_{max} and $AUC_{(0-24)}$). The MTD from Study E7080-E044-101 (25 mg QD) was correlated with higher drug exposure compared with the MTD from Study E7080-A001-102 (10 mg BID).

Consequently, 25 mg QD was selected for the future studies, as it was determined to be the safest dose that provides the highest efficacy. To simplify the dose reduction scheme, a dosage of 24 mg QD (two 10 mg capsules + one 4 mg capsule) was selected for continued lenvatinib development. Refer to the respective IBs/approved labeling for detailed background information on pembrolizumab and lenvatinib.

Combination therapy:

The dosing regimen for lenvatinib was selected based on the results of Phase 1b portion of Phase 1b/2 Study 111/KEYNOTE-146, the primary endpoints of which was to determine the MTD and RP2D of lenvatinib in combination with pembrolizumab 200 mg Q3W. Thirteen participants (lenvatinib 24 mg/day + pembrolizumab 200 mg Q3W: n=3; lenvatinib 20 mg/day + pembrolizumab 200 mg Q3W: n=10) were enrolled in the Phase 1b portion of the study. Eight of the participants had RCC, 2 had NSCLC, 2 had EC, and 1 had melanoma. There were 2 DLTs at the dose of lenvatinib 24 mg/day + pembrolizumab 200 mg Q3W (1 participant had Grade 3 arthralgia, and another had Grade 3 fatigue); hence, this dose 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 antitumor efficacy and tolerable safety profile seen in both the EC 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 SOC Chemotherapy

Doses and regimens for SOC chemotherapy were selected based on standard clinical practice and should be prepared per local and institutional guidelines according to the approved product labels.

4.3.4 Maximum Dose Exposure for This Study

NOTE: In alignment with the study-specific investigator letter dated 05-SEP-2024, all participants should discontinue the combination of lenvatinib + pembrolizumab or lenvatinib monotherapy, as applicable. On a case-by-case basis, investigators may contact the Sponsor

for consideration of continuing lenvatinib + pembrolizumab or lenvatinib monotherapy if they assess the participant is deriving clinical benefit.

The maximum dose/exposure of lenvatinib monotherapy is 24 mg QD and maximum dose/exposure of lenvatinib when given in combination with pembrolizumab is 20 mg QD. Lenvatinib may be continued until disease progression or until a discontinuation criterion is met.

The maximum dose/exposure of pembrolizumab allowed in this study is 200 mg IV Q3W for approximately 2 years (35 cycles) of initial treatment (Section 8.1.8).

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), or the last participant on active treatment is consented in the extension study. 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.

The Sponsor estimates that the maximum duration of the study from first participant entered through long-term follow-up will be approximately 5 years.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age, 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.

Male or female participants with R/M HNSCC who have progressed after platinum-containing chemotherapy at any time (with or without cetuximab) and a PD-1/PD-L1 inhibitor and are at least 18 years of age may be enrolled in this study.

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

Demographics

1. Be male or female and at least 18 years of age on the day of providing documented informed consent.
2. Have pathologically confirmed recurrent (not amenable to curative treatment with local and/or systemic therapies) or metastatic (disseminated) HNSCC of the oral cavity, oropharynx, hypopharynx, and/or larynx that is considered incurable by local therapies.

   Note: Other primary tumor sites of HNSCC, including nasopharynx (any histology) or unknown primary tumor (including p16+ unknown primary), are not eligible.
3. Have experienced disease progression at any time during or after treatment with a platinum-containing (eg, carboplatin or cisplatin) regimen with or without cetuximab.
4. Have disease progression on or after treatment with an anti-PD-1/PD-L1 mAb administered either as monotherapy, or in combination with other checkpoint inhibitors or other therapies. Anti-PD-1/PD-L1 treatment progression is defined by meeting <u>all</u> the following criteria:
   - Treatment with an anti-PD-1/PD-L1 mAb.
   - Has received at least 2 doses of an anti-PD-1/PD-L1 mAb.
   - Has demonstrated disease progression on or after an anti-PD-1/PD-L1 mAb as defined by RECIST 1.1.

- Progressive disease has been documented within 12 weeks from the last dose of anti-PD-1/PD-L1 mAb.

  Note: Eligible participants may have received anti-PD-1/PD-L1 mAb and platinum-containing therapy concomitantly.

5. Have submitted pre-study imaging that demonstrates evidence of disease progression based on investigator review of at least 2 pre-study images per RECIST 1.1, following initiation of treatment with a PD-1/PD-L1 inhibitor.

   Note: These pre-study images must be submitted to the iCRO for verification that they are of acceptable diagnostic quality. The iCRO must have received these images and verified that they are of acceptable diagnostic quality before randomization.

   Note: The pre-study imaging submitted to the iCRO will be from disease progression on or after treatment with an anti-PD-1/PD-L1 mAb; NOT from images associated with disease progression on or after platinum-containing chemotherapy given sequentially.

6. Have documentation of results from testing of HPV status for oropharyngeal cancer defined as p16 IHC testing using the CINtec® p16 Histology assay and a 70% cutoff point. Refer to Section 8.8.2 for details. If HPV status has previously been tested using this procedure, no retesting is required.
7. Have provided tissue for PD-L1 biomarker analysis from a core or excisional biopsy (fine needle aspirate is not adequate) not previously irradiated. Repeat samples may be required if adequate tissue is not provided. A newly obtained biopsy (within 90 days prior to start of study treatment) is strongly preferred, but an archival sample is acceptable.

8. Have measurable disease by CT or MRI based on RECIST 1.1 as verified by BICR. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

9. Have an ECOG performance status of 0 or 1 assessed within 7 days of the first dose of study intervention.

Male Participants

10. Male participants are eligible to participate if they agree to the following during the intervention period and for at least:

- 1 week after the last dose of lenvatinib; 3 months after the last dose of capecitabine and paclitaxel; and 6 months after the last dose of docetaxel. No male contraception is needed for pembrolizumab and cetuximab.

  - See Appendix 7 for country-specific requirements.

- Refrain from donating sperm

PLUS either:

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

  OR

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

  Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

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

- If the contraception requirements in the local label for any of the study drugs is less stringent than the requirements above, the local label requirements should be followed.

Female Participants

11. 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 randomized to lenvatinib + pembrolizumab (Arm 1) or lenvatinib monotherapy (Arm 3) and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with lower 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 1 month post lenvatinib, 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 randomized to SOC chemotherapy is eligible to participate if she is using a contraceptive method that is highly effective with low user dependency or abstinent from heterosexual intercourse as her preferred and usual lifestyle and agrees not to donate or freeze/store eggs during the intervention period and for at least 6 months after the last dose of capecitabine, docetaxel, paclitaxel; and 2 months after the last dose of cetuximab.

- 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 5.

- Abstains from breastfeeding during the study intervention period and for at least 180 days after the last dose of chemotherapy, 1 month after the last dose of lenvatinib, or 120 days after the last dose of pembrolizumab.

- 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.

- If the contraception requirements in the local label for any of the study drugs is less stringent than the requirements above, the local label requirements should be followed.

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

Informed Consent

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

Additional Categories

13. Have adequately controlled BP with or without antihypertensive medications, defined as BP ≤150/90 mm Hg with no change in antihypertensive medications for at least 1 week prior to randomization.
14. Have adequate organ function as defined in Table 1.
    - **Note:** Specimens must be collected within ≤7 days prior to the start of study intervention.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[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

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

[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.

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

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

15. Participants who are HBsAg positive are eligible if they have received HBV antiviral therapy for at least 4 weeks and have undetectable HBV viral load prior to randomization.

    Note: Participants should remain on anti-viral therapy throughout study intervention and follow local guidelines for HBV anti-viral therapy post completion of study intervention.

    Hepatitis B screening tests are not required unless:

    - Known history of HBV infection
    - As mandated by local health authority

16. Participants with history of HCV infection are eligible if HCV viral load is undetectable at screening.

    Note: Participants must have completed curative anti-viral therapy at least 4 weeks prior to randomization.

    Hepatitis C screening tests are not required unless:

    - Known history of HCV infection
    - As mandated by local health authority

5.2 Exclusion Criteria

An individual must be excluded from the study if the individual meets any of the following criteria:

Medical Conditions

1. Removed, redundant with Inclusion Criterion #2.
2. 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.
3. Has disease that is suitable for local therapy administered with curative intent.
4. Has a life expectancy of less than 3 months and/or has rapidly progressing disease (eg, tumor bleeding, uncontrolled tumor pain), in the opinion of the treating investigator.
5. Has any evidence of symptoms or signs of active tumor bleeding within 6 months prior to randomization.
6. Has ulceration and/or fungation of disease onto the skin surface.
7. 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.
8. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
9. Has an active infection requiring systemic therapy.
10. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.

11. 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.

12. Has a known additional malignancy that is progressing or has required active systemic treatment within the past 3 years.

    - **Note:** Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, superficial bladder cancer, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded. Participants with low-risk early stage prostate cancer defined as follows are not excluded; Stage T1c or T2a with a Gleason score ≤ 6 and prostatic-specific antigen (PSA) <10 ng/mL either treated with definitive intent or untreated in active surveillance that has been stable for the past year prior to study enrollment. Other exceptions may be considered after consultation with the Sponsor.

13. Has an active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease-modifying agents, corticosteroids or immunosuppressive drugs).

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

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

15. Has a known history of human immunodeficiency virus (HIV) infection.

    Note: No HIV testing is required unless mandated by local health authority.

16. Removed, not relevant due to addition of Inclusion Criteria #15 and #16.

17. Has a history of any contraindication or has a severe hypersensitivity to any components of pembrolizumab (≥Grade 3), lenvatinib or SOC chemotherapy.

18. Has pre-existing ≥Grade 3 gastrointestinal or non-gastrointestinal fistula

19. Has a history of a gastrointestinal malabsorption or any other condition or procedure that may affect oral study drug absorption.

20. Has had major surgery within 3 weeks prior to first dose of study interventions.

    - **Note:** Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility.

- **Note:** Participants must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study therapy.

21. Has clinically significant cardiovascular impairment within 12 months of the first dose of study drug, such as history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction or cerebrovascular accident /transient ischemic attack (TIA)/stroke, cardiac revascularization, or cardiac arrhythmia associated with hemodynamic instability.

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

22. Has active tuberculosis.

23. Has difficulty swallowing capsules or ingesting a suspension orally or by a feeding tube.

Prior/Concomitant Therapy

24. Participants previously treated to one of the 4 SOC agents in this trial (ie, docetaxel, paclitaxel, capecitabine, or cetuximab) may not receive the same agent if randomized to the SOC chemotherapy arm.

25. Has had prior treatment with lenvatinib as monotherapy or in combination with an PD-1/PD-L1 inhibitor or other therapies.

26. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to Study Day 1 or has not recovered (ie, ≤ Grade 1 or baseline) from AEs due to a previously administered agent. Participants with endocrine-related AEs Grade ≤2 requiring treatment or hormone replacement may be eligible.

    - **Note:** Events of ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia or laboratory values listed in Table 1 are allowed.

    - **Note:** Participants must have recovered from all radiation-related toxicities and not have had radiation pneumonitis.

    - **Note:** As per section 6.5.1, anticancer therapies are prohibited during screening.

27. Has received a live or live attenuated vaccine within 30 days prior to the first dose of study intervention.

    Note: Administration of killed vaccines is allowed.

    Refer to Section 6.5.1 for information on COVID-19 vaccines.

28. Was previously treated with 4 or more systemic regimens given for R/M disease.

Prior/Concurrent Clinical Study Experience

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

Diagnostic Assessments

30. Has urine protein ≥1 g/24 hours.

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

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

32. Has a LVEF below the institutional (or local laboratory) normal range, as determined by MUGA or ECHO.

Other Exclusions

33. Has a history or current evidence of any condition, therapy, or laboratory abnormality that may 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, in the opinion of the treating investigator.

34. Has a known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.

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 consent will not be replaced.

6 STUDY INTERVENTION

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

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

6.1 Study Intervention(s) Administered

NOTE: In alignment with the study-specific investigator letter dated 05-SEP-2024, all participants should discontinue the combination of lenvatinib + pembrolizumab or lenvatinib monotherapy, as applicable. On a case-by-case basis, investigators may contact the Sponsor for consideration of continuing lenvatinib + pembrolizumab or lenvatinib monotherapy if they assess the participant is deriving clinical benefit. Treatment with SOC chemotherapy (Arm 2) can continue at the discretion of the investigator until a protocol specified discontinuation criterion is met.

The study intervention(s) to be used in this study are outlined in Table 2.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1	Experimental	Lenvatinib	Drug	Capsule	10 mg 4 mg	20 mg	Oral	Once daily	Test Product	IMP	Central
Arm 1	Experimental	Pembrolizumab	Biological/Vaccine	Solution	25 mg/mL	200 mg	IV Infusion	Day 1 of each 3-week cycle	Test Product	IMP	Central
Arm 2	Active Comparator	Docetaxel	Drug	Solution	20 mg/mL	75 mg/m^2	IV Infusion	Day 1 of each 3-week cycle	Comparator	IMP	Provided centrally by the Sponsor or locally by the study site.
Arm 2	Active Comparator	Capecitabine	Drug	Tablet	150 mg 500 mg	1250 mg/m^2	Oral	BID (Twice a day) on Day 1 to 14 of each 3-week cycle	Comparator	IMP	Provided centrally by the Sponsor or locally by the study site.
Arm 2	Active Comparator	Paclitaxel	Drug	Solution	6 mg/mL	80 mg/m^2	IV Infusion	Day 1, 8, and 15 of each 3-week cycle	Comparator	IMP	Provided centrally by the Sponsor or locally by the study site.

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 2	Active Comparator	Cetuximab	Biological/Vaccine	Solution	2 mg/mL 5 mg/mL	400 mg/m^2 loading dose followed by 250 mg/m^2	IV Infusion	Day 1, 8, and 15 of each 3-week cycle	Comparator	IMP	Provided centrally by the Sponsor or locally by the study site.
Arm 3	Experimental	Lenvatinib	Drug	Capsule	10 mg 4 mg	24 mg	Oral	Once daily	Test Product	IMP	Central

EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product.
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.

NOTE: Unit dose strength of SOC chemotherapy may vary based on the local guidelines.

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

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

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

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

Lenvatinib is provided as capsules for oral administration and does not require preparation. For participants unable to swallow capsule, a suspension can be prepared. If a lenvatinib dose is missed and cannot be taken within 12 hours of the scheduled dosing time, the participant should skip this dose and take the next dose at the scheduled time the next day. Refer to the Lenvatinib Pharmacy Manual for additional information.

Chemotherapy should be prepared per local and institutional guidelines according to the approved product labels.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention allocation will occur centrally using an IRT system. Participants will be assigned randomly in a 3:3:2 ratio to the lenvatinib + pembrolizumab, SOC chemotherapy or lenvatinib monotherapy arms, respectively. Randomization will continue until the planned number of participants in each arm receive at least 1 dose of study medication.

6.3.2 Stratification

Randomization will be stratified according to the following factors:

1. PD-L1 tumor expression as determined by PD-L1 immunohistochemistry (TPS <50% versus ≥50%)

2. ECOG performance status (0 versus 1)

6.3.3 Blinding

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

However, the independent radiologist(s) who perform the central imaging review will be blinded to the participant's treatment group assignment.

The investigator will be blinded to the participant-level biomarker results.

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 intervention plan for >28 days for lenvatinib or >12 weeks due to toxicity reasons for pembrolizumab and >6 weeks from the last dose due to administrative reasons for pembrolizumab require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management. Please refer to Section 8.1.8.2 for compliance of study drug administration.

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:

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.
>
> Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

If the investigator determines that a participant requires any of the following prohibited medications and vaccinations for any reason during the study, study intervention 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
  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.

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 30 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.

Note: All prior anticancer agents will be collected and recorded on the case report form (CRF) during the Screening visit (eg, first-line, second-line, third-line, etc).

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

6.5.1 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment periods of this study:

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

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

2. Other concurrent investigational drugs.

3. Live or live attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study. Administration of killed vaccines is allowed.

4. Systemic glucocorticoids are permitted only for the following purposes:

    - Physiologic doses of corticosteroids not exceeding 10 mg daily of prednisone equivalent may be used during the study.

    - Brief, limited use (≤7 days) of systemic corticosteroids is permitted when considered Standard of Care (eg, for exacerbation of chronic obstructive pulmonary disease).

    - To modulate symptoms of an AE that is suspected to have an immunologic etiology

    - As needed for the prevention of emesis

    - Premedication of IV contrast allergies

- In addition, the following glucocorticoid use is allowed:

    - For topical or ocular use

    - Intraarticular joint use

    - For inhalation in the management of asthma or COPD

    - **Note: For participants on lenvatinib monotherapy or SOC chemotherapy arms, the use of systemic glucocorticoids on-study treatment is acceptable**.

5. Radiation therapy.

Participants who, in an assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be discontinued from study treatment.

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

See Appendix 7 for country-specific requirements.

Please refer to USPI (or local product label) for additional guidance.

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/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.

See Appendix 7 for country-specific requirements.

Please refer to USPI (or local product label) for additional guidance.

6.5.3 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. For participants receiving lenvatinib + pembrolizumab, suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined in Table 4 along with the lenvatinib dose modification guidelines in Table 3. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab or lenvatinib.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the pembrolizumab treatment guidance. Refer to Table 3 for guidelines regarding lenvatinib dose modification and supportive care.

Premedication(s) for docetaxel, paclitaxel, cetuximab, or capecitabine will be given as per SOC. Corticosteroid pretreatment or post-treatment of docetaxel and paclitaxel is acceptable in concordance with the local label or SOC. It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

6.6 Dose Modification (Escalation/Titration/Other)

NOTE: In alignment with the study-specific investigator letter dated 05-SEP-2024, all participants should discontinue the combination of lenvatinib + pembrolizumab or lenvatinib monotherapy, as applicable. On a case-by-case basis, investigators may contact the Sponsor for consideration of continuing lenvatinib plus pemrolizumab or lenvatinib monotherapy if they assess the participant is deriving clinical benefit. Treatment with SOC chemotherapy (Arm 2) can continue at the discretion of the investigator until a protocol specified discontinuation criterion is met. Participants who are continuing study treatment should follow the modified protocol study procedures as specified in this amendment.

Adverse events will be graded using NCI CTCAE version 5.0. 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.

Refer to Section 6.6.2 for dose modification guidance for overlapping toxicity for the pembrolizumab + lenvatinib combination.

Participants who interrupt or discontinue 1 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).

6.6.1 Lenvatinib Dose Modification and Toxicity Management

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

The starting dose of lenvatinib is 24 mg/day for monotherapy (Arm 3) and 20 mg/day in combination with pembrolizumab (Arm 1). Dose reductions of lenvatinib occur in succession based on the previous dose level (Arm 3: 24, 20, 14, and 10 mg/day; Arm 1: 20, 14, 10, and 8 mg/day). Any dose reduction below 8 mg/day must be discussed with the Sponsor. Once the lenvatinib dose has been reduced, it may not be increased at a later date, unless the dose has been mistakenly decreased; in this situation, the Sponsor's approval is required to increase the dose.

Refer to the subsections below for management of hypertension (Section 6.6.1.1), proteinuria (Section 6.6.1.2), diarrhea (Section 6.6.1.3), hepatotoxicity (Section 6.6.1.4), thromboembolic events (Section 6.6.1.5), PRES/RPLS (Section 6.6.1.6), hypocalcemia (Section 6.6.1.7), hemorrhage (Section 6.6.1.8), gastrointestinal perforation of fistula formulation (Section 6.6.1.9), QT prolongation (Section 6.6.1.10) and ONJ (Section 6.6.1.11) as appropriate, before consulting the dose modification table (Table 3).

Table 3 Dose Modification Guidelines for Lenvatinib-Related Adverse Events

Treatment-Related Toxicity[a,b]	**Management**	**Dose Adjustment**
Grade 1 or Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c, d] or Grade 3[e,g]		
First occurrence	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Arm 3: Reduce lenvatinib dose to 20 mg once a day (1-level reduction) Arm 1: 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	Arm 3: Reduce lenvatinib dose to 14 mg once a day (1-level reduction) Arm 1: 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	Arm 3: Reduce lenvatinib dose to 10 mg once a day (1-level reduction) Arm 1: Reduce lenvatinib dose to 8 mg once a day (1-level reduction)
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib	Discuss with Sponsor
Grade 4[f]: Discontinue Study Treatment		

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

Note: For grading, see CTCAE version 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] Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

[g] For Grade 3 thromboembolic event, permanently discontinue lenvatinib. See Section 6.6.1.5.

6.6.1.1 Management of Hypertension

Hypertension is a recognized side effect of treatment with drugs inhibiting VEGF signaling. Investigators should therefore ensure that participants enrolled to receive treatment with lenvatinib have BP of ≤150/90 mm Hg at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before C1D1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Regular assessment of BP should be as detailed in the SoA (Sections 1.3.1, 1.3.2, and 1.3.3). 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 with significant risk factors for severe complications (eg, BP ≥160/100 mm Hg, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant co-morbidities). Once the participant has been on the same antihypertensive medications for at least 48 hours and the BP is controlled, lenvatinib should be resumed as described below.

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

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):

1. Institute appropriate medical management

2. Discontinue study drug

6.6.1.2 Management of Proteinuria

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

Detection and Confirmation

1. Perform urine dipstick testing or urinalysis per the SoA (Section 1.3.1, 1.3.3 and 1.3.4). 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 or urinalysis result is ≥2+ (≥100 mg/dL).

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

Grading of Proteinuria

- Grading according to NCI CTCAE 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 3.

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

6.6.1.3 Management of Diarrhea

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

6.6.1.4 Management of Hepatotoxicity

Liver function tests (ALT, AST, bilirubin levels) should be conducted as detailed in the SoA (Section 1.3) and as clinically indicated. If signs/symptoms indicating liver injury occur, instructions contained in Table 3 should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure occurs, the study drug must be discontinued. If hepatic failure (any grade per CTCAE version 5) occurs, lenvatinib must be discontinued.

6.6.1.5 Management of Thromboembolic Events

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

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

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

PRES/RPLS is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. MRI is necessary to confirm the diagnosis of PRES/RPLS. Appropriate measures should be taken to control BP. In participants with signs or symptoms of PRES/RPLS, instructions in Table 3 should be followed.

6.6.1.7 Management of Hypocalcemia

Serum calcium should be monitored per the SoA (Section 1.3). Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v5.0, using the following formula:

$$\text{Corrected calcium} = ([4 - \text{serum albumin in g/dL}] \times 0.8 + \text{serum calcium})$$

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

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

6.6.1.8 Management of Hemorrhage

Instructions in Table 3 should be followed for the management of hemorrhage. Either resume at a reduced dose or discontinue lenvatinib depending on the severity and persistence of hemorrhage.

6.6.1.9 Management of Gastrointestinal Perforation or Fistula Formation

Lenvatinib should be discontinued in any participants who develop gastrointestinal perforation of any grade or Grade 4 fistula. Refer to Appendix 7 for country-specific requirement.

6.6.1.10 Management of QT Prolongation

Lenvatinib should be withheld in the event of development of QT interval prolongation greater than 500 msec. Lenvatinib should be resumed at a reduced dose when QTc prolongation is resolved to <480 msec or baseline. Monitor potassium, calcium and magnesium, and replenish as appropriate.

6.6.1.11 Management of Osteonecrosis of the Jaw

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

6.6.2 Dose Modifications for Overlapping Toxicities

Based on the known toxicity profiles of pembrolizumab and lenvatinib, certain treatment-related AEs are uniquely associated with one drug versus the other. For example, hypertension, arterial thrombotic events, proteinuria, and hemorrhagic events are known risks

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

1. Timing of AE onset

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

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

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

2. Severity of AE

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

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

   a. ALT or AST >5 X ULN for more than 2 weeks.
   Pembrolizumab will have already been permanently discontinued per Table 4, but lenvatinib may be administered at a reduced dose by the time this criterion is met and must be permanently discontinued immediately.

   b. ALT or AST >3 X ULN and (TBL >2 X ULN or INR >1.5).
   Although Table 4 advises pembrolizumab to be withheld (interrupted), and Table 3 advises lenvatinib to have no dose modification or a reduction, if this criterion is met, both drugs must be permanently discontinued immediately.

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

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

6.6.3 Pembrolizumab Dose Modifications

Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity. Pembrolizumab may be interrupted for a maximum of 12 weeks. An interruption of study treatment for more than 12 weeks due to toxicity or more than 6 weeks from the last dose due to administrative reasons will require Sponsor approval before study intervention can be resumed (see Section 6.4).

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

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

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

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 4.

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

General instructions:

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

irAEs	Toxicity Grade (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	
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

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[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	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
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		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
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		
Myocarditis	Assymptomatic 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		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue 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 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

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

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

6.6.3.2 Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

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

Table 5 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

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

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Abbreviations: h = hour; hrs = hours; IV = intravenous(ly); NSAIDs = nonsteroidal anti-inflammatory drugs; PO = oral(ly); Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE) at http://ctep.cancer.gov		

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.

Pembrolizumab may be interrupted for situations other than treatment-related AEs, such as medical/surgical events or logistical reasons not related to study intervention. Participants should be placed back on study intervention within 6 weeks of the last dose administered, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the participant's study record. Imaging should not be delayed for delays in treatment cycles.

6.6.5 Dose Modification for Standard Treatment Chemotherapy

Doses of SOC chemotherapy below should be based upon actual body weight, not ideal body weight. If the participant's weight increases or decreases by >10% from baseline during the course of the study, the drug dose should be re-calculated.

6.6.5.1 Dose Selection for Docetaxel (Preparation)

The preparation and administration of docetaxel should follow local treatment guidelines. Refer to the USPI (or local product label) for additional supportive care guidance.

Corticosteroid use with docetaxel

In order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reaction, all participants randomized to receive docetaxel must be premedicated with oral corticosteroids such as dexamethasone 16 mg per day (eg, 8 mg BID) for 3 days starting 1 day prior to docetaxel administration.

6.6.5.2 Dose Modifications for Docetaxel

Participants who are dosed initially at 75 mg/m^2 and who experience either febrile neutropenia, neutrophils <500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions, or other Grade 3/4 non-hematological toxicities during docetaxel treatment should have treatment withheld until resolution of the toxicity and then resumed at 55 mg/m^2. Participants who develop ≥Grade 3 peripheral neuropathy should have docetaxel treatment discontinued entirely.

Docetaxel should be administered only if ANC >1500/mm^3 (1.5 x 10^9/L) and platelets >100,000/mm^3 (100 x 10^9/L).

Docetaxel should not be given to participants with bilirubin >ULN, or to participants with AST and/or ALT >1.5 x ULN with concomitant alkaline phosphatase >2.5 x ULN as participants with laboratory values above these limits are at increased risk of SAEs (refer to local product label).

For additional guidance regarding treatment modification of docetaxel, please refer to the USPI (or local prescribing information) for dose modifications for hematologic and other non-hematologic toxicities as recommended for monotherapy with docetaxel in participants with non-small cell lung cancer.

6.6.5.3 Dose Selection for Paclitaxel (Preparation)

The preparation and administration of paclitaxel should follow local treatment guidelines. Refer to the USPI (or local product label) for additional supportive care guidance.

Premedication for paclitaxel

All participants should be premedicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg PO administered approximately 12 and 6 hours before paclitaxel, diphenhydramine (or its equivalent) 50 mg IV 30 to 60 minutes prior to paclitaxel, and cimetidine (300 mg) or ranitidine (50 mg) IV 30 to 60 minutes before paclitaxel.

6.6.5.4 Dose Modifications for Paclitaxel

The following guidelines should be followed for dose modifications for AEs that are suspected to be caused by paclitaxel.

- Paclitaxel should be administered only if ANC >1500/mm^3 (1.5 x 10^9/L) and platelets >100,000/mm^3 (100 x 10^9/L).

- In case of a life-threatening event, consider discontinuing paclitaxel.

In case of Grade 3 or 4 AEs despite medical management:

- Hold paclitaxel until the event has resolved to Grade 1 or better, then re-introduce at the reduced dose of 65 mg/m^2.

- In case of a second episode of the same event at Grade 3 or 4, consider discontinuing paclitaxel.

- In cases of Grade 2 non-hematologic AE (except alopecia) that are persistent despite medical management, consider holding paclitaxel until event resolves to Grade 1 or better, then re-introduce at a reduced dose.

- The minimum paclitaxel dose allowed on study and the first dose reduction level is 65 mg/m^2 (ie., only one dose reduction of paclitaxel is permitted to 65 mg/m^2).

For additional guidance regarding treatment modification of paclitaxel, please refer to the USPI (or local prescribing information) for dose modifications for hematologic and other non-hematologic toxicities.

6.6.5.5 Dose Selection for Cetuximab (Preparation)

Participants receiving cetuximab should be premedicated with an H1 antagonist (eg, 50 mg of diphenhydramine) intravenously 30-60 minutes prior to the first dose. Premedication for subsequent doses of cetuximab should be given per medical judgment and history of prior infusion reactions. See Appendix 7 for country-specific requirements.

Guidelines for medical therapy for infusion reactions detailed in Table 6 are provided below for reactions due to cetuximab.

Refer to the USPI (or local product label) for additional supportive care guidance.

6.6.5.6 Dose Modifications for Cetuximab

Reduce, delay, or discontinue cetuximab to manage adverse reactions as described in Table 6 below.

Table 6 Cetuximab Dose Modifications for Adverse Reactions

Adverse Reaction	**Severity[a]**	**Dosage Modification**
Infusion reactions [see USPI Warnings and Precautions (5.1)]	Grade 1 or 2	Reduce the infusion rate by 50%.
	Grade 3 or 4	Immediately and permanently, discontinue cetuximab.
Dermatologic toxicities and infections sequelae (eg, acneiform rash, mucocutaneous disease) [see USPI Warnings and Precautions (5.4)]	1st occurrence; Grade 3 or 4	Delay infusion 1 to 2 weeks; if condition improves, continue at 250 mg/m^2. If no improvement, discontinue cetuximab.
	2nd occurrence; Grade 3 or 4	Delay infusion 1 to 2 weeks; if condition improves, continue at 200 mg/m^2. If no improvement, discontinue cetuximab.
	3rd occurrence; Grade 3 or 4	Delay infusion 1 to 2 weeks; if condition improves, continue at 150 mg/m^2. If no improvement, discontinue cetuximab.
	4th occurrence; Grade 3 or 4	Discontinue cetuximab.

Adverse Reaction	Severity[a]	Dosage Modification
Pulmonary toxicity [see USPI Warnings and Precautions (5.3)]	Acute onset or worsening pulmonary symptoms	Delay infusion 1 to 2 weeks; if condition improves, continue at the dose that was being administered at the time of occurrence. If no improvement in 2 weeks or interstitial lung disease (ILD) is confirmed, discontinue cetuximab.
[a] National Cancer Institute (NCI) Common Toxicity Criteria (CTC) version 2.0. Source: Adapted from ERBITUX® USPI: ImClone LLC a wholly-owned subsidiary of Eli Lilly and Company.		

For additional guidance regarding treatment modification of cetuximab, please refer to the USPI (or local prescribing information) for dose modifications for hematologic and other non-hematologic toxicities.

6.6.5.7 Dose Selection for Capecitabine (Preparation)

The preparation and administration of capecitabine should follow local treatment guidelines. Capecitabine should be administered at 1250 mg/m^2 twice daily orally (ie., total daily dose of 2500 mg/m^2), for 14 days continuously, followed by 7 days with no dosing in a 3-week cycle.

Capecitabine can induce diarrhea, sometimes severe, including necrotizing enterocolitis (typhlitis). Therefore, for participants who experience capecitabine-associated diarrhea, aggressive supportive management with anti-diarrheals, including loperamide and lomotil, according to local SOC treatment guidelines are indicated. Refer to the USPI (or local product label) for additional supportive care guidance.

6.6.5.8 Dose Modifications for Capecitabine

Recommended dose modifications for capecitabine are outlined in Table 7.

Table 7 Recommended Dose Modifications for Capecitabine

Toxicity NCIC Grades	During a Course of Therapy	Dose Adjustment for Next Treatment (% of Starting Dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
• 1st appearance	Interrupt until resolved to Grade 0-1	100%
• 2nd appearance		75%
• 3rd appearance		50%
• 4th appearance	Discontinue treatment permanently	-

Toxicity NCIC Grades	During a Course of Therapy	Dose Adjustment for Next Treatment (% of Starting Dose)
Grade 3		
• 1st appearance	Interrupt until resolved to Grade 0-1	75%
• 2nd appearance		50%
• 3rd appearance	Discontinue treatment permanently	-
Grade 4		
• 1st appearance	Discontinue permanently OR If physician deems it to be in the participant's best interest to continue, interrupt until resolved to Grade 0-1	50%

NCIC=National Cancer Institute of Canada.
Source: XELODA® USPI; Hoffmann-La Roche, Inc.© 2019 Genentech, Inc.

If unscheduled laboratory assessments during a treatment cycle show Grade 3 or 4 hematologic toxicity, treatment with capecitabine should be interrupted.

For additional guidance regarding treatment modification of capecitabine, please refer to the USPI (or local prescribing information) for dose modifications for hematologic and other non-hematologic toxicities.

6.7 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 lenvatinib or lenvatinib monotherapy, if available.

6.8 Clinical Supplies Disclosure

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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 prior to 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 8.10.4 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. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 1.3 and Section 8.10.4.

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

  - ALT or AST >5 × ULN for more than 2 weeks
    Pembrolizumab will have already been permanently discontinued per Table 4 but lenvatinib may be administered at a reduced dose by the time this criterion is met and must be permanently discontinued immediately.

  - ALT or AST >3 × ULN and (TBL >2 × ULN or INR >1.5)
    Although Table 4 advises pembrolizumab to be withheld (interrupted), Table 3 advises lenvatinib to have no dose modification or a reduction, if this criterion is met, both drugs must be permanently discontinued immediately.

- The participant 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.
- Progressive disease is radiographically documented per RECIST 1.1 and centrally verified.
  - As of Amendment 07, central tumor response assessments will no longer be performed. Participants receiving study treatment will be assessed locally by the investigator for disease progression per the protocol schedule. Scans will not be sent to the iCRO.
    - Participants with RECIST 1.1 disease progression per local investigator assessment must discontinue study treatment.
- Continuing initial treatment beyond centrally verified radiographic PD per RECIST 1.1 may be permitted, following Sponsor consultation, only for participants randomized to the lenvatinib + pembrolizumab arm. This is also applicable for participants on Crossover treatment receiving lenvatinib + pembrolizumab that have experienced locally assessed radiographic PD per RECIST 1.1. As of Amendment 07, participants continuing lenvatinib + pembrolizumab on initial or crossover treatment may be permitted to continue treatment beyond locally assessed radiographic PD per RECIST 1.1, following Sponsor consultation.

  NOTE: The participant must be deriving clinical benefit from the study therapy per investigator assessment and meet these additional criteria:

  - Absence of unacceptable toxicity
  - Absence of clinical symptoms or signs indicating clinically significant disease progression
  - No decline in performance status
  - Absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g., CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention

- NOTE: Participants who experience centrally verified PD in the lenvatinib monotherapy or SOC chemotherapy arms can crossover to receive lenvatinib + pembrolizumab at time of disease progression with Sponsor consultation. As of Amendment 07, participants in the SOC chemotherapy arm or lenvatinib monotherapy arm may not crossover to receive lenvatinib + pembrolizumab at the time of disease progression.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.
- NOTE: Exceptions to second malignancy include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, new nonulcerated primary melanoma <1 mm in depth with no nodal involvement, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy. Exceptions should be discussed with the Sponsor before continuing therapy or follow-up.
- The participant has any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6.

- Administrative reasons requiring cessation of treatment.

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.
- 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.

Prior to entering Cross over, participant must provide documented informed consent.

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention allocation/randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant 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.

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.

8.1.5.3 Prior Anticancer Therapy for HNSCC

The investigator or qualified designee will review and record all prior anticancer treatments including systemic treatments, radiation, and surgeries, regardless of the time before the first dose of study intervention. This will include platinum-containing chemotherapy with or without an anti-PD-1/PD-L1 therapy.

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.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

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

8.1.8 Study Intervention Administration

Study intervention should begin within 3 days of randomization. Lenvatinib may be administered at home except on C1D1, C1D15 and C2D1; on these days, lenvatinib will be taken in the clinic. Administration of study interventions will be monitored by the investigator and/or study staff. Study intervention will be administered by the investigator and/or study staff according to the specifications within 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.

Investigators must choose a standard treatment (docetaxel, paclitaxel, cetuximab, or capecitabine) prior to randomization and document the selection in the trial database (See data entry guidelines). When choosing a standard therapy, the investigator should refer to the USPI or local product label (with special consideration for any contraindications, special warnings and precautions of use).

8.1.8.1 Timing of Dose Administration

Lenvatinib

Lenvatinib is provided as capsules for oral administration and does not require preparation. Lenvatinib 24 mg (two 10-mg capsules and one 4-mg capsule) for monotherapy and lenvatinib 20 mg (two 10-mg capsules) for combination therapy will be taken orally with water (with or without food) once daily at approximately the same time each day in each 21-day cycle. However, on C1D1 and C2D1, lenvatinib will be administered in the clinic 0-4 hours after completion of pembrolizumab administration. Participants should not take their study medication on C2D1 before their appointment.

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

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 feeding tube. See the Pharmacy Manual for additional information.

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 C1D1, pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each subsequent cycle due to administrative reasons.

Docetaxel

Docetaxel can be administered on Day 1 of each 3-week cycle.

- **Day 1 of each 3-week cycle:**
  Trial treatment of docetaxel should be administered on Day 1 of each 3-week cycle after all procedures/assessments have been completed as detailed on the SoA (Section 1.3.2). Docetaxel 75 mg/m^2 will be administered as an IV infusion administered over 1 hour or following local SOC.

Paclitaxel

Trial treatment of paclitaxel should be administered on Days 1, 8 and 15 of each 3-week cycle after all procedures/assessments have been completed as detailed on the SoA (Section 1.3.2). Paclitaxel 80 mg/m^2 will be administered as an IV infusion administered over 1 hour or following local SOC**.**

Cetuximab

Trial treatment of cetuximab should be administered on Days 1, 8 and 15 of each 3-week cycle after all procedures/assessments have been completed as detailed on the SoA (Section 1.3.2).

Cetuximab will be given as an initial loading dose on C1D1 of 400 mg/m^2 infused over 120 minutes (maximum infusion rate 10 mg/min). For all subsequent doses, starting with C1D8, administer 250 mg/m^2 infused over 60 minutes (maximum infusion rate 10 mg/min) or follow local SOC.

Capecitabine

Trial treatment of capecitabine should be administered twice daily on Days 1 to 14 of each 3-week cycle after all procedures/assessments have been completed as detailed on the SoA (Section 1.3.2).

Capecitabine will be administered at an initial dose of 1250 mg/m^2. Administration of capecitabine dissolved in water or through a feeding tube will be allowed for participants unable to swallow tablets.

8.1.8.2 Compliance

Lenvatinib

Sites should collect and record the number of lenvatinib capsules returned, per the SoA (Section 1.3). 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.

Pembrolizumab, docetaxel, paclitaxel or cetuximab:

Study intervention will be administered by the investigator and/or study staff according to the specifications within the protocol and Pharmacy Manual, as applicable. The total volume of study intervention infused will be compared with the total volume prepared to determine compliance with each dose administered.

Capecitabine:

Site staff will perform tablet counts at regular intervals during treatment, per the SoA (Section 1.3.2). Capecitabine compliance will be calculated by the Sponsor, based on the drug accountability documented by the site staff and monitored by the Sponsor/designee. 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 and Section 8.10.4.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the discontinuation visit (EOT visit) should be performed at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.10 Participant Blinding/Unblinding

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

8.1.11 Calibration of Equipment

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

8.1.12 Demographics

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

8.1.13 Tumor Tissue for Biomarker Status

During the Screening period, a tissue sample is required for each participant consisting of:

- 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 Central Laboratory Manual.

The PD-L1 result will be masked 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 07: All participants who are still on study treatment 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.

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.

Scans should include the head and neck, chest, and abdomen at all timepoints specified in Section 1.3. Scans of the brain and pelvis are optional (if clinically indicated). For an individual participant, scans should be consistent at all timepoints, (ie, follow-up scans should image the same areas as the baseline area, using the same imaging modality).

At screening, participant eligibility will require radiographic documentation of at least one lesion that meets the requirements for selection as a target lesion, as defined by RECIST 1.1 verified by BICR, prior to participant randomization.

All scheduled scans for participants from the sites will be submitted to the iCRO. In addition, a scan (including via other modalities) 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 perform expedited verification of radiologic PD and communicate the results to the study site and Sponsor via email. In clinically stable participants, scans 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). Once PD is verified centrally, subsequent scans (if acquired) should not be submitted to the iCRO.

8.2.1.1 Pre-study Scans to Confirm Disease Progression

The site's study team must have reviewed and submitted pre-study scans that are of diagnostic quality from at least 2 dates to determine that radiographic progression has occurred per RECIST 1.1 following initiation of prior PD-1/PD-L1 inhibitor treatment. Scans should include:

- The baseline scan for prior anti-PD-1/PD-L1 or a scan showing nadir during prior anti-PD-1/PD-L1 treatment.
- Scans showing PD on or after an anti-PD-1/PD-L1 mAb (minimum of 2 doses; within 12 weeks of last dose of pre-study treatment).

The iCRO must have received these scans prior to randomization in this study and must also verify that the scans are of diagnostic quality prior to randomization. These scans will be collected by the iCRO for possible retrospective independent review of response.

8.2.1.2 Initial Tumor Scans

Initial scans must be performed within 28 days prior to the date of randomization. The site study team must review screening scans to confirm that the participant has measurable disease per RECIST 1.1. Additionally, expedited verification of measurable disease based on RECIST 1.1 by BICR at screening will be used to determine participant eligibility prior to randomization. Verification by the BICR that the participant's scans show at least 1 lesion that is appropriate for selection as a target lesion per RECIST 1.1 is required prior to participant randomization.

If brain scans are required to document the stability of existing metastases, the brain MRI should be acquired during Screening period. Scans performed as part of routine clinical management is acceptable for use as a baseline tumor scan if it is of diagnostic quality and performed within 28 days prior to the date of randomization and can be assessed by the iCRO.

Note: The pre-study scan demonstrating progression on prior PD-1/PD-L1 treatment can be used as the screening scan for the study if it is performed within 28 days before the date of randomization and can be assessed by the iCRO.

8.2.1.3 Tumor Scans During the Study

The first on study scan assessment should be performed at Week 6 (42-49 days) from the date of randomization. Subsequent scans should be performed every 6 weeks (42 days ±7 days) or more frequently if clinically indicated. After 1 year (48 weeks), participants who remain on study intervention will have their scans performed every 9 weeks (63 days ±7 days). Scan timing should follow calendar days from randomization and not be adjusted for delays in cycle starts. Scans should continue to be performed until PD is identified by the investigator and verified by BICR (unless the investigator elects to continue study intervention and the Sponsor is consulted), the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first. All supplemental scans must be submitted to the iCRO if imaging shows PD or to support response assessments.

Treatment beyond centrally verified radiographic PD per RECIST 1.1 may be permitted at the discretion of the investigator after consultation with the Sponsor and receiving informed consent. Participants who continue treatment beyond centrally verified radiographic PD must continue 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.

Scans to confirm PR or CR should be performed at the next scheduled scan or at least 4 weeks after the first indication of a response is observed. If participants confirmed PR or CR outside of their regular scheduled scan, they will then return to the regular scan schedule,

starting with the next scheduled scan time point. Participants who receive additional scans for confirmation do not need to undergo the next scheduled scan if it is less than 4 weeks later; scans may resume at the subsequent scheduled scan time point.

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

8.2.1.4 End of Treatment and Follow-up Tumor Scans

As of Amendment 07: 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.For participants who discontinue study intervention, scans should be performed at the time of study intervention discontinuation (±4-week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, a scan at study intervention discontinuation is not mandatory. For participants who discontinue study intervention due to centrally verified PD, this is the final required scan. All scans should be submitted to the iCRO.

For participants who discontinue study intervention without centrally verified PD, every effort should be made to continue monitoring disease status by scans using the same scan schedule as during study intervention calculated from the date of randomization (every 6 weeks in Year 1 or every 9 weeks after Year 1), until the start of new anticancer treatment, centrally verified PD, pregnancy, death, withdrawal of consent, or the end of the study, or notification by the Sponsor, whichever occurs first.

8.2.1.5 Crossover Treatment Tumor Scans

As of Amendment 07: Imaging scans will no longer be submitted to the iCRO. Additionally, participants in the SOC chemotherapy arm or lenvatinib monotherapy arm may not crossover to receive lenvatinib + pembrolizumab at the time of disease progression. Original protocol text that is contained in this section has been retained for reference.

Participants who experience centrally verified PD in the lenvatinib monotherapy or SOC chemotherapy arms can cross over to lenvatinib + pembrolizumab at time of centrally verified disease progression with Sponsor consultation. The Crossover screening scans (new baseline) should be performed within 28 days prior to the first dose as new baseline scan. The centrally verified PD scan in initial treatment may also be used as the Crossover baseline scan if it is within 28 days prior to the Crossover first dose. During Crossover, the first scan should be performed 6 weeks (42-49 days) after Crossover C1D1. Subsequent scans should be performed every 6 weeks (42 days ±7 days) or more frequently if clinically indicated. After 1 year (48 weeks), participants who remain on study intervention will have their scan performed every 9 weeks (63 days ±7 days). Scan timing should follow calendar days from Crossover C1D1 and not be adjusted for delays in cycle starts. For participants who discontinue Crossover treatment, scans should be performed at the time of study intervention discontinuation (±4 week window). If a previous scan was obtained within 4 weeks before the date of discontinuation, a scan at study intervention discontinuation is not mandatory. Scans should continue to be performed until PD is identified by the investigator per RECIST

1.1, the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first. All supplemental scans must be submitted to the iCRO if imaging shows PD or to support response assessments. All Crossover scans should be submitted to the iCRO for quality control, storage, and possible retrospective review.

8.2.1.6 Second Course Scans

NOTE: As of Amendment 07, there will be no Second Course Scans. This section is no longer applicable.

8.2.1.7 RECIST 1.1 Assessment of Disease

As of Amendment 07: Central tumor response assessments will be discontinued. 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.

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

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

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

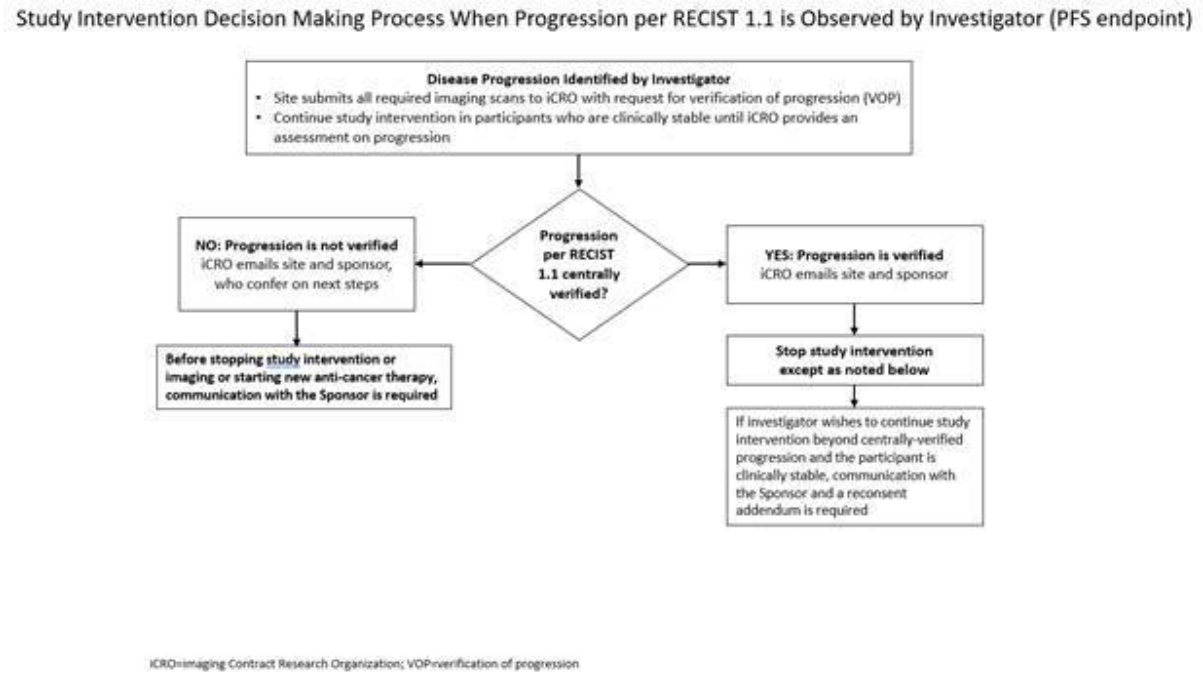
If disease progression is verified, the process continues as follows:

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

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

Figure 2 Study Intervention Decision Making Process (PFS)



iCRO = Imaging Contract Research Organization; PFS = Progression-free Survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1

8.2.2 Patient Reported Outcomes

As of Amendment 07: 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:

- Prior to dosing at C1D1, and then
- Day 1 of every cycle from C1 through C9, then
- Day 1 of every other cycle through C17 (C9, C11, C13, C15, C17), then
- Every 3 cycles through C35 (C20, C23, C26, C29, C32, C35)
- Obtain at EOT and Safety FU.

If the EOT visit happens prior to 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 prior to drug administration, AE evaluation, and disease status notification. If the participant does not complete the ePROs at a scheduled time point, the MISS_MODE form must be completed to capture the reason the assessment was not performed.

8.3 Safety Assessments

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 Central Laboratory Manual.

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

8.3.1 Physical Examinations

A complete physical examination including oral examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. Comprehensive physical examinations will be performed as specified in the SoA (Section 1.3). A comprehensive physical examination will include evaluations of

the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination.

A brief directed physical examination including oral examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. Directed physical examinations will be performed as specified in the SoA (Section 1.3).

Documentation of the physical examination will be included in the source documentation at the investigational site. Significant findings prior to participant treatment allocation will be recorded on the appropriate CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the appropriate CRF. Height will only be measured and recorded at Screening.

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

8.3.2 Vital Signs

The investigator or qualified designee will take vital signs (using a validated method) at Screening, before the administration of each dose of study intervention and during the Safety Follow-up Period, as specified in the SoA (Section 1.3). Vital signs include body temperature, heart rate, respiratory rate, weight, and blood pressure.

BP and heart rate will be measured after the participant has been resting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

Only 1 BP measurement is needed for participants with systolic BP <140 mm Hg and diastolic BP <90 mm Hg. If the participant's initial BP 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.

At the C1D8 telephone visit and if required between clinic visits, participants will have BP measured. If the participant does not return to the study site for this BP measurement, BP may be measured, for example, at home or at a local pharmacy, and the results will be reviewed with the investigator or designee. The investigator/site may provide a diary as a tool to aid the participant in collecting BP evaluations between clinic visits. The Sponsor will not provide diaries to the site. If BP result raises concerns, the investigator may require additional follow-up, including an on-site BP re-test, or other clinically appropriate intervention(s).

8.3.3 Electrocardiograms

ECGs will be obtained as designated in the SoA (Section 1.3). Additional time points may be performed as clinically necessary. Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Participants must be in the recumbent position for a period of 5 minutes prior to the ECG. The Fridericia correction method for calculating QTc will be used.

QTc prolongation has been seen in some lenvatinib studies. Drugs known to prolong the QTc interval (including Class Ia and III antiarrhythmics) must be used cautiously. Please refer to lenvatinib prescribing information. Monitor electrocardiograms every cycle (as specified in the SoA) in participants with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Please refer to the lenvatinib IB.

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

8.3.4 Echocardiograms or Multigated Acquisition Scans

A MUGA scan (using a technetium-based tracer) or an ECHO can be performed to further assess LVEF as designated in the SoA (Sections 1.3.1 and 1.3.2). Additional time points may be performed as clinically necessary. MUGA or ECHO scans should be performed locally in accordance with the institution's standard practice. MUGA scans are the preferred modality. However, whichever modality is used for the initial assessment should be repeated for all subsequent LVEF assessments for that participant. LVEFs as assessed by the institution will be entered on the eCRF. Investigator assessment will be based on institutional reports.

8.3.5 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the 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 for all AEs and 90 days for all SAEs (or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever occurs first) after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.5.1 CBC with Differential and Clinical Chemistry

CBC with differential and clinical chemistry results must be reviewed before administration of study intervention. Electrolytes such as potassium, calcium, and magnesium should be monitored and abnormalities, when considered clinically significant, should be corrected in all participants before starting study intervention.

8.3.5.2 Urine Dipstick Testing/Urinalysis

After Cycle 1, urine dipstick testing will only be performed in participants taking lenvatinib as described in SoA (Section 1.3). Urine dipstick testing for participants with ≥2+ proteinuria should be monitored as described in Section 6.6.1.2.

8.3.5.3 Thyroid Function Testing

The screening blood sample for thyroid function testing will be obtained within 7 days before the first dose of study intervention.

Thyroid function testing will be performed within 7 days of C1D1 and 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.

8.3.6 Pregnancy Testing

Pregnancy testing ([urine or serum] as required by local regulations) should be conducted according to Section 1.3 (SoA) and at the end of relevant systemic exposure for all arms.

- Pregnancy testing requirements for study inclusion are described in Section 5.1.
- Pregnancy testing (urine or serum) should be conducted at monthly intervals during intervention.
- Pregnancy testing (urine or serum) should be conducted for the time it takes to eliminate systemic exposure after the last dose of study intervention(s) as noted in Section 5.1, ie, 120 days following cessation of pembrolizumab, 30 days following cessation of lenvatinib, or 180 days following cessation of chemotherapy.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3.7 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 8) 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.

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

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

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

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

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention allocation/randomization, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention allocation/randomization through 30 days following cessation of study intervention must be reported by the investigator.

- All AEs meeting serious criteria, from the time of intervention allocation/randomization through 90 days following cessation of study intervention or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention randomization through the time required to eliminate systemic exposure after cessation of study intervention as described in Sections 5.1 and 8.3.6, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside 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

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

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

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities 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.

Note: To meet EU CTR requirements, the Sponsor will report SUSARs to the Eudravigilance database via E2B(R3) electronic ICSR form in compliance with CTR 536/2014.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee), or a pregnancy that occurs during the study in a nonparticipant whose sexual partner is a participant capable of producing ejaculate is reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as

serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Pembrolizumab

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

Lenvatinib

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

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

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 8.4.1.

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

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the participants in the study. Any suspected endpoint that upon review is not progression of the cancer under study will be forwarded to Global Pharmacovigilance as an SAE within 24 hours of determination that the event is not progression of the cancer under study.

8.4.7 Events of Clinical Interest

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 lenvatinib overdose without an associated adverse event is not considered an ECI.
2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow up of these criteria can be found in the Investigator 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
- SOC chemotherapy: ≥20% over the prescribed dose

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

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

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.”

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

8.6 Pharmacokinetics

As of Amendment 07: Sample collection for PK and/or ADA, RNA analysis, and plasma/serum biomarkers is discontinued. Original protocol text that is contained in this section has been retained for reference.

Blood samples will be collected as specified in the SoA (Sections 1.3.1 and 1.3.3). Study sites must have appropriately trained staff and adequate equipment for procuring and

processing specimens. Instructions for collection, handling and shipping of PK samples will be provided in the Central Laboratory Manual.

To evaluate the immunogenicity and exposure of pembrolizumab in this indication, blood samples for PK and ADA will be collected and may be stored only at this time. Further analysis may be performed if required and reported separately if conducted.

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

8.6.1 Blood Collection for Serum Pembrolizumab

To evaluate pembrolizumab immunogenicity and pembrolizumab exposure in this combination with lenvatinib, sample collections for analysis of ADA and PK are currently planned as shown in the SoA (Section 1.3). Blood samples will be obtained to measure PK and ADA of serum pembrolizumab. These samples collected may be stored at this time. Analysis may be performed if required. If ongoing ADA and/or PK results are deemed to be unnecessary by the Sponsor, it may be decided to discontinue or reduce further sample collection in this study. If PK and/or ADA analyses are performed, the results of these analyses will be reported separately.

8.6.2 Blood Collection for Plasma Lenvatinib

To evaluate the exposure of lenvatinib when administered as monotherapy and when co-administered with pembrolizumab blood samples will be collected from all participants as specified in the SoA (Section 1.3). Plasma concentrations of lenvatinib will be measured and quantified by validated tandem high-performance liquid chromatography/mass spectroscopy methods. Data will be analyzed using a PopPK approach.

8.6.3 Blood Collection for RNA Analysis and Plasma and Serum Biomarker Analysis

Blood for RNA Analysis: Collect predose on C1D1, C2D1, C3D1, C5D1, and at EOT.

Blood for Plasma Biomarkers: Collect at predose on D1 of C1, C2, C3, C5, C7, C9, C11, C13, C15, C17, then on D1 of every 3 cycles until EOT, including at the EOT visit.

Blood for Serum Biomarkers: Collect predose on C1D1, C1D15, C2D1, C3D1, C5D1, and at EOT.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

As of Amendment 07: 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

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

8.8.1 Planned Genetic Analysis Sample Collection

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

The planned genetic analysis sample should be obtained predose on Day 1 but may be collected at the next scheduled blood draw, if needed. Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the Central Laboratory Manual.

8.8.2 Human Papilloma Virus Testing

Participants with oropharynx cancer must have assessment of HPV status from tumor tissue prior to randomization as per the inclusion criteria (Section 5.1).

Tumor p16 expression must be evaluated by assessment of IHC analysis with CINtec® p16 Histology assay (Ventana Medical Systems Inc., Tucson AZ) using positive p16 expression, which is defined as strong and diffuse nuclear and cytoplasmic staining in 70% or more of the tumor cells.

Note: If local p16 testing results are not available, or cannot be assessed by the specified method, a tumor tissue sample may be submitted for p16 testing at the designated central laboratory.

Note: Oral cavity, hypopharynx, and larynx cancer are not required to undergo HPV testing by p16 IHC as by convention they are assumed to be HPV negative.

8.9 Health Economics 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 following cessation of study intervention, or 30 days following cessation of study intervention, if the participant initiates new anticancer therapy, whichever is earlier.

8.10 Visit Requirements

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

8.10.1 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.

See Appendix 7 for country-specific requirements

8.10.2 Initial Treatment Phase

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

8.10.2.1 Telephone Contact or Visit

A telephone visit will be scheduled on C1D8 to report blood pressure and record AEs, as outlined in the SoA (Section 1.3). At the C1D8 telephone visit and if required between clinic visits, participants will have BP measured. If the participant does not return to the study site for this BP measurement, BP may be measured, for example, at home or at a local pharmacy, and the results will be reviewed with the investigator or designee. The investigator/site may provide a diary as a tool to aid the participant in collecting BP evaluations between clinic visits. The Sponsor will not provide diaries to the site. If BP result raises concerns, the investigator may require additional follow-up, including an on-site BP re-test, or other clinically appropriate intervention(s).

8.10.2.2 Addition of Pembrolizumab Following Progression on Lenvatinib Monotherapy

An investigator may add pembrolizumab to lenvatinib monotherapy following centrally verified PD by RECIST 1.1 with Sponsor consultation. The lenvatinib dose should be decreased to 20 mg daily (from 24 mg monotherapy) when given in combination with pembrolizumab. If the lenvatinib dose was reduced during monotherapy, the reduced dose should be continued. Visit requirements are outlined in the SoA (Section 1.3.3). As of Amendment 07, participants in the lenvatinib monotherapy arm may not crossover to receive lenvatinib + pembrolizumab at the time of disease progression.

Participants may receive pembrolizumab alone during Crossover with Sponsor consultation. Participants who discontinue lenvatinib prior to initiation of Crossover treatment will not restart lenvatinib.

8.10.3 Second Course

NOTE: As of Amendment 07, there will be no Second Course. This section is no longer applicable.

8.10.4 Discontinued Participants Continuing to be Monitored in the Study

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

8.10.5 Posttreatment Visit

8.10.5.1 Safety Follow-up Visit

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

Participants who are eligible for Crossover treatment may have up to 2 Safety Follow-up visits, 1 after initial treatment or First Course and 1 after the Crossover treatment.

8.10.5.2 Efficacy Follow-up Visits

As of Amendment 07: Efficacy Follow-up Visits will be discontinued. Therefore, participants in efficacy follow-up and survival follow-up should be discontinued from the study. 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.

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than centrally verified PD will begin

Efficacy Follow-up and should be assessed as outlined in the SoA corresponding to the assigned treatment arm (Section 1.3) to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, centrally verified PD, death, end of study, or the participant begins retreatment as detailed in Section 8.10.3. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter Survival Follow-up.

8.10.5.3 Survival Follow-up Contacts

As of Amendment 07: Survival Follow-up Visits will be discontinued. Those participants remaining on study treatment at the time of Amendment 07 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.

8.10.6 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.

If a participant withdraws consent, vital status (survival information) may be obtained by review of public records, in accordance with local regulations.

If a participant is lost to follow-up, vital status (survival information) can be conducted by review of medical records or public records when vital status is in question in accordance with local regulations.

9 STATISTICAL ANALYSIS PLAN

NOTE: A periodic review of safety data using a data cutoff date of 31-MAY-2024 was conducted by the eDMC. At the request of the eDMC, OS data were provided for review, though there was no preplanned statistical analysis for OS. At this safety analysis, the OS Kaplan-Meier curves did not favor pembrolizumab + lenvatinib versus SOC chemotherapy. Based on these data and the recommendation of the eDMC, Amendment 07 was implemented to discontinue the combination of lenvatinib + pembrolizumab or lenvatinib monotherapy arms. The prespecified interim and final analyses of the study described in Section 9 will not be performed. Selected analyses of safety endpoints will be performed at the end of the study; there will be no further analyses of efficacy or ePRO endpoints.

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to the conduct of any analysis, will be documented in an sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR. The PRO analysis plan will also be included in the sSAP. Other planned analyses (ie, those specific to the analysis of PK data) are beyond the scope of this document or will be documented in separate analysis plans.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2 through 9.12.

Study Design Overview	Phase 2 study of lenvatinib (E7080/MK-7902) with pembrolizumab (MK-3475) versus SOC chemotherapy and lenvatinib monotherapy in participants with R/M HNSCC who have progressed after platinum chemotherapy and after treatment with immunotherapy (PD-1/PD-L1 inhibitors)
Treatment Assignment	Approximately 400 participants will be randomized in a 3:3:2 ratio into 3 treatment arms: lenvatinib + pembrolizumab combination therapy (Arm 1), SOC chemotherapy (Arm 2) and lenvatinib monotherapy (Arm 3). As of Amendment 07, 408 participants have been randomized and no additional participants will be randomized. Stratification factors are as follows: • ECOG performance status (0 vs. 1) • PD-L1 tumor expression as determined by PD-L1 immunohistochemistry (TPS <50% vs. ≥50%) This study will be conducted as an open-label study.
Analysis Populations	Efficacy: ITT Safety: All Participants as Treated (APaT)
Primary Endpoint(s)	OS
Key Secondary Endpoints	• PFS per RECIST 1.1 based on BICR • OR per RECIST 1.1 based on BICR

Statistical Methods for Key Efficacy Analyses	The HRs of OS and PFS 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. ORR will be estimated by treatment group with 95% CI calculated by Clopper-Pearson exact method. The difference in ORR and its 95% CI from the stratified Miettinen and Nurminen method with strata weighting by sample size will be provided.
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 unstratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].
Interim Analysis	CCI [redacted]
Multiplicity	
Sample Size and Power	

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.

This study is being conducted as a randomized, open-label study, i.e., participants, investigators, and Sponsor personnel will be aware of participant study intervention assignments after each participant is enrolled and study intervention is assigned.

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

Although the trial is open-label, analyses or summaries generated by randomized intervention assignment, or actual intervention received will be limited and documented. In addition, the independent radiologist(s) will perform the central imaging review without knowledge of treatment group assignment.

9.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3.

9.4 Analysis Endpoints

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

9.4.1 Efficacy Endpoints

Primary

- **Overall Survival (OS):** defined as time from randomization to death due to any cause.

Secondary

- **Progression-free Survival (PFS):** defined as time from randomization to the first documented disease progression per RECIST 1.1 by BICR or death due to any cause, whichever occurs first.

    - **Objective Response (OR):** the OR is defined as a confirmed complete response (CR) or partial response (PR) per RECIST 1.1 as assessed by BICR.

    - **Duration of Response (DOR):** for participants who demonstrate CR or PR, DOR is defined as the time from 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 and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory values and vital signs.

9.4.3 Patient Reported Outcome Endpoints

As of Amendment 07, PRO endpoints will not be analyzed.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Population

The efficacy analyses for OS, PFS and ORR will be based on the ITT population. All randomized participants will be included in this population. Participants will be analyzed in the treatment group to which they are randomized.

The analysis population for DOR consists of all responders.

9.5.2 Safety Analysis Population

Safety Analyses will be conducted in the APaT population, which consists of all randomized participants who received at least one dose of study intervention. Participants will be included in the treatment group corresponding to the study intervention they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who take incorrect study intervention for the entire treatment period; such participants will be included in the treatment group corresponding to the study intervention actually received. Participants who are randomized to the SOC chemotherapy arm can receive different chemotherapies at investigator's choice, and they will be pooled and analyzed under SOC chemotherapy arm.

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

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analyses

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

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.

For the lenvatinib monotherapy arm, if it continues to 100 participants following the interim futility analysis, summary statistics for the lenvatinib monotherapy will be provided for each endpoint according to the plan as outlined below.

The stratification factors used for randomization (see Section 6.3.2) will be applied to all stratified analyses, in particular, stratified Cox model.

The efficacy analyses for ORR, DOR and PFS will be based on responses and documented progression events that occur prior to protocol-specified treatment Crossover.

9.6.1.1 Overall Survival

The non-parametric Kaplan-Meier method will be used to estimate the OS curve by treatment group.

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. Participants without documented death at the time of analysis will be censored at the date the participant was last known to be alive.

9.6.1.2 Progression-Free Survival

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve by treatment group.

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.

CCI

CCI

[redacted]

9.6.1.3 Objective Response Rate

The difference in ORR and its 95% CI from the stratified Miettinen and Nurminen method with strata weighting by sample size will be provided. 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].

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 CR or PR 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 why responding participants are censored will also be provided. CCI

[redacted]

CCI

[redacted]

9.6.1.5 Analysis Strategy for Key Efficacy Variables

A summary of the primary analysis strategy for the key efficacy endpoints for the lenvatinib + pembrolizumab combination therapy and SOC chemotherapy is provided in Table 11.

Table 11 Summary of Analysis Strategy for Efficacy Endpoints

Endpoint	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint			
OS	• HR estimation using stratified Cox model with Efron's tie handling method	ITT	Censored at last date the participant was known to be alive
Secondary Endpoints			
PFS per RECIST 1.1, BICR	• HR estimation using stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 9.
ORR per RECIST 1.1 by BICR	• Estimation: Clopper-Pearson (exact) method	ITT	Participants with missing data are considered non-responders

Endpoint	Statistical Method	Analysis Population	Missing Data Approach
DOR per RECIST 1.1, BICR	Summary statistics using Kaplan-Meier method	Responders in ITT population	Censored according to rules in Table 10.

Abbreviations: BICR = Blinded independent central review; DOR = Duration of response; HR= hazard ratio; ITT= intention-to-treat; ORR = Objective response rate; OS = Overall survival; PFS = Progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumors.

9.6.2 Statistical Methods for Safety Analyses

The primary safety analyses will include only events that occur prior to protocol-specified treatment crossover.

9.6.2.1 Overall Safety Assessment

The overall safety evaluation will include a summary by treatment group of the number and percentage of participants with at least one AE, drug-related AE, serious AE, serious drug-related AE, Grade 3-5 AE, drug-related Grade 3-5 AE, discontinuation from study intervention due to an AE, interruption of study intervention due to an AE, an AE resulting in dose reduction, and an AE resulting in death.

The number and percentage of participants with specific AEs will also be provided. Point estimate and 95% CIs for the difference between the lenvatinib + pembrolizumab combination therapy arm (Arm 1) and SOC chemotherapy arm (Arm 2) in the percentage of participants with specific AEs will be provided for AEs that occur in at least 10% of participants in any treatment group. The threshold of at least 10% of participants was chosen 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, difference between Arm 1 and Arm 2 in the percentage of participants with specific Grade 3-5 AEs (≥ 5% of participants in any treatment group), SAEs (≥5% of participants in any treatment group), and tumor hemorrhage (incidence ≥4% of participants in 1 of the treatment groups) will also be summarized by point estimate and 95% CI. Rainfall plots with point estimates and 95% CIs will be displayed for Arm 1 and Arm 2 with specific AEs, specific Grade 3-5 AEs and specific SAEs that meet the corresponding predefined threshold rules.

CIs for between treatment group differences will be provided using the M&N method [Miettinen, O. and Nurminen, M. 1985]. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as helpful descriptive measures for the review of the safety profile and not as a formal method for assessing the statistical significance of the between-group differences.

The number and percentage of participants with laboratory toxicity grade increased from baseline will be summarized by the post-baseline maximum toxicity grade per CTCAE V5.0 for each gradable laboratory test.

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

9.6.2.2 Assessment of Safety Topics of Special Interest

AEs that are immune-mediated or potentially immune-mediated are considered safety topics of special interest (AEOSI) in this study. These events have been characterized consistently throughout the pembrolizumab clinical development program. Point estimates and 95% CIs for between-group difference is not expected to add value to the safety evaluation, and hence only number and percentage of participants with such pembrolizumab AEOSI will be provided, as well as the number and percentage of participants with corticosteroids administration to treat an AEOSI. Summary statistics will be provided for the analysis of time from first dose to the onset of an AEOSI.

Table 12 summarizes the analysis strategy for safety endpoints in this study.

Table 12 Analysis Strategy for Safety Parameters

Analysis Part	Safety Endpoint	Descriptive Statistics	95% between-group CI (Graphical display)
Overall Safety Assessment	Specific AEs (incidence ⩾10% of participants in any treatment group)	X	X
	Specific Grade 3-5 AE (incidence ⩾5% of participants in any treatment group)	X	X
	Specific serious AE (incidence ⩾5% of participants in any treatment group)	X	X
	Tumor hemorrhage (incidence ≥ 4% of participants in 1 of the treatment groups)	X	X
	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 of study treatment due to AE	X	
	Interruption of study treatment due to AE	X	
	AE that resulted in dose reduction	X	
	AE that resulted in death	X	
	Laboratory toxicity grade increase from baseline	X	
	Change from baseline results (vital signs)	X	
Assessment of safety topics of special interest	Pembrolizumab AEOSI Lenvatinib CSAE	X	
Abbreviations: AE = adverse event; AEOSI = adverse event of special interest; CSAE = clinically significant adverse event; CI = confidence interval.			

9.6.3 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

CCI

[redacted]

9.8 Multiplicity

CCI

[redacted]

9.9 Sample Size and Power Calculations

CCI

[redacted]

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the treatment effect for OS, PFS, and ORR (with a nominal 95% CI) will be estimated for lenvatinib + pembrolizumab combination therapy and SOC chemotherapy arms within each category of the following subgroup variables:

- PD-L1 tumor expression as determined by PD-L1 immunohistochemistry (TPS <50% vs. ≥50%)
- ECOG performance status (0 vs. 1)
- Age category (<65 vs. ≥65 years)
- Sex (female vs. male)
- Race (white vs. all others)
- Geographic region of enrolling site (US vs. Western Europe vs. ROW)
- PD-L1 tumor expression as determined by PD-L1 immunohistochemistry (CPS < 1 vs. ≥ 1)
- Anti-PD-1/PD-L1 treatment prior to study entry (most recent vs. not most recent)

A forest plot will be produced, which provides the estimated point estimates and CIs 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 will be conducted using the unstratified Miettinen and Nurminen method.

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

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, SOC chemotherapy 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 Interventional Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), Regulation (EU) 536/2014, the International Council for Harmonisation Good Clinical Practice (ICH -GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Input may be considered from a broad range of stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and healthcare providers to ensure operational feasibility. Trial design also includes proactive identification of critical to quality factors utilizing a risk-based

approach. Plans are then developed to assess and mitigate risks to those factors as appropriate during the trial. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD 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 potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its

trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on medical record 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 their 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 their 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 their 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.

The Sponsor has EU-approved Binding Corporate Rules since 2017, covering all aspects of its Global Privacy Program (Corporate Policy 20), and is self-certified pursuant to the EU-US Data Privacy Framework.

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 Scientific Advisory Committee (SAC)

This study was developed in collaboration with a 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 upon any recommendations made by the DMC regarding the study.

10.1.4.3 External Data Monitoring Committee

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

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7.2) 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 trials Regulation 536/2014, 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, https://euclinicaltrials.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 Regulation 536/2014 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 Regulation 536/2014, 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.

For investigators located in countries with serious breach reporting requirements, investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol which is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

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 (eg, EU CTR: 25 years after the end of the study). 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 13 will be performed by the local laboratory.
- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine or serum) should be conducted at monthly intervals during intervention.
  - Pregnancy testing (urine or serum) should be conducted at the end of relevant systemic exposure and correspond with the time frame for female participant contraception in Section 5.1.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator, to establish the absence of pregnancy at any time during the participant's participation in the study.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 13 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	WBC count with Differential[a] Neutrophils Lymphocytes Monocytes Eosinophils Basophils		
Chemistry	BUN[b]	Urea	Uric acid	Creatinine[c]
	AST(SGOT)	ALT(SGPT)	Alkaline phosphatase	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Potassium	Magnesium	Sodium	Calcium[d]
	Albumin	Bicarbonate or Carbon Dioxide (CO_2)[e]	Chloride	Phosphorous
	Glucose (nonfasting)	Total Protein		
	Lipase	Amylase		
Thyroid function	TSH	T3 or FT3	T4	
Coagulation[f]	PT (INR) aPTT or PTT			

Laboratory Assessments	Parameters
Routine Urinalysis[g]	• Specific gravity • pH, glucose, protein[h], hemoglobin or blood, ketones, by dipstick
Other Tests	• Follicle-stimulating hormone (as needed in WONCBP only) • Highly sensitive serum or urine β human chorionic gonadotropin (β hCG) pregnancy test • Serology (HIV antibody, HbsAg, and HCV RNA). Required at baseline only if mandated by local health authority.

Abbreviations: ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); β HCG = β human chorionic gonadotropin; BUN = blood urea nitrogen; CPK = creatine phosphokinase; FT3 = free triiodothyronine; GFR = glomerular filtration rate; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCV, mean corpuscular volume; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cells; RNA = ribonucleic acid; T3 = triiodothyronine; T4 = thyroxine, TSH = thyroid-stimulating hormone; ULN = upper limit of normal; UPCR = urine protein-to-creatinine; WBC = white blood cell; WOCBP = women of childbearing potential; WONCBP = women of non-childbearing potential.

[a] Absolute or % acceptable per institutional standard.
[b] Urea is acceptable if BUN is not available as per institutional standard
[c] GFR (measured or calculated) or creatinine clearance can be used in place of creatinine.
[d] Corrected calcium should be checked for participants with hypoalbuminemia.
[e] Bicarbonate performed only if considered local standard of care.
[f] Performed as part of the screening assessment and as clinically indicated for participants taking anticoagulants
[g] If urine dipstick testing suggests a urinary tract infection, or if clinically indicated, a urine microscopy, culture, and sensitivity should be performed at the institution's laboratory.
[h] If urine protein is ≥2+ (first occurrence or a subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level), then a 24-hour urine collection or an immediate spot urine protein-to-creatinine (UPCR) test should be done to quantify the 24-hour urine protein excretion. A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when UPCR is ≥2.4.

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

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

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

Misuse

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

Abuse

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

Lenvatinib overdose without an associated adverse event is not reportable as an AE. Refer to Section 8.5 for the definition of overdose.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

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

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

a. Results in death
b. Is life-threatening

   The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization

   Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is

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

d. Results in persistent or significant disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported

Additional events that require reporting in the same manner as SAE

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

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

10.3.5 Recording AE and SAE

AE and SAE recording

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

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

Assessment of intensity/toxicity

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

    - The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 5.0 Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

    - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

    - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.

    - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

    - Grade 4: Life threatening consequences; urgent intervention indicated.

    - Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame.

The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- The following components are to be used to assess the relationship between the Sponsor's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

  - **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

  - (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?

  - If yes, did the AE recur or worsen?

  - If yes, this is a positive rechallenge.

  - If no, this is a negative rechallenge.

  (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

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

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to 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 Sponsor's product relationship).

    - Yes, there is a reasonable possibility of Sponsor's product relationship:

        - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

    - No, there is not a reasonable possibility of Sponsor's product relationship:

        Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- 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

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

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

  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

A high 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] • Intrauterine hormone-releasing system (IUS) • Non-hormonal IUD Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

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

Not applicable.

10.7 Appendix 7: Country-specific Requirements

10.7.1 Canada

6.6.1.9 Management of Gastrointestinal Perforation or Fistula Formation

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

10.7.2 UK

5.1 Inclusion Criteria

- Inclusion Criterion #10: Male participants are eligible to participate if they agree to at least 6 months of contraception after the last dose of paclitaxel.

6.5.1 Prohibited Concomitant Medications

- Live vaccines are to be avoided for 120 days after last dose pembrolizumab.

6.5.1 Prohibited Concomitant Medications and 6.5.2 Drug Interactions

Paclitaxel

- Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (eg, ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce CYP2C8 or CYP3A4 (eg, rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine).

Docetaxel

- Concomitant use of docetaxel with strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) should be avoided.

Capecitabine

- Care should be exercised when capecitabine is co-administered with CYP2C9 substrates.

6.6.5.5 Dose Selection for Cetuximab (Preparation)

- Close monitoring of participants is required during the infusion for cetuximab, particularly during the first administration.

10.7.3 France

6.5.1 Prohibited Concomitant Medications

- In participants being treated with lenvatinib, invasive dental procedures should be avoided during treatment with lenvatinib.

- Caution should be exercised when lenvatinib is used either simultaneously or sequentially with antiresorptive therapy (eg, denosumab and bisphosphonates) and/or other angiogenesis inhibitors.

8.10.1 Screening

- A dental examination and appropriate preventive dental care should be considered prior to initiation of lenvatinib.

10.7.4 Romania

5.1 Inclusion Criteria

- Inclusion Criterion #10: Male participants are eligible to participate if they agree to at least 6 months of contraception after the last dose of paclitaxel.

10.7.5 Portugal

5.1 Inclusion Criteria

- Inclusion Criterion #10: Male participants are eligible to participate if they agree to at least 6 months of contraception after the last dose of paclitaxel.

10.7.6 Norway

5.1 Inclusion Criteria

- Inclusion Criterion #10: Male participants are eligible to participate if they agree to at least 6 months of contraception after the last dose of paclitaxel.

10.8 Appendix 8: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all selfcare, but unable to carry out any work activities. Up and about >50% of waking hours.
3	In bed >50% of the time. Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead.
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
1L	first-line
2L	second-line
5-FU	5-fluorouracil
β-HCG	β human chorionic gonadotropin
ADA	antidrug antibodies
AE(s)	adverse event(s)
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
APaT	all participants as treated
AST	aspartate aminotransferase
BICR	blinded independent central review
BID	twice a day
BOR	best overall response
BP	blood pressure
BUN	blood urea nitrogen
CI	confidence interval
C_{max}	maximum or peak serum concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CPS	combined positive score
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
ctNA	circulating tumor nucleic acid
CXDY	Cycle X Day Y
D/C	discontinuation
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLT(s)	dose-limiting toxicity(ies)
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
EC	endometrial cancer
ECG	electrocardiogram
ECHO	echocardiogram
ECI	events of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data collection
eDMC	external Data Monitoring Committee
ELISA	enzyme-linked immunoassay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 items

Abbreviation	Expanded Term
EORTC QLQ-H&N35	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Head and Neck Module
EOT	end of treatment
ePRO	electronic patient reported outcomes
EQ-5D-5L	European Quality of Life Five-Dimensional Five-Level Questionnaire
EuroQol	European Quality of Life
FAS	Full Analysis Set
FDA	Food and Drug Administration (United States of America)
FDAAA	Food and Drug Administration Amendments Act
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FSH	follicle-stimulating hormone
FT3	free triiodothyronine
FU	follow-up
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HPV	human papilloma virus
HR	hazard ratio
HRQoL	health-related quality of life
HRT	hormone replacement therapy
HUVEC	human umbilical vein endothelial cell
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCR	iRECIST complete response
iCRO	imaging contract research organization
ICSR	Individual Case Safety Report
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IMP	investigational medicinal product
INR	international normalized ratio
IO	immuno-oncology
iPR	iRECIST partial response
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	Response Evaluation Criteria in Solid Tumors Version 1.1 for immune-based therapeutics
IRT	interactive response technology
iSD	iRECIST stable disease
ITT	intention-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
IVD	in vitro diagnostic
LAM	lactational amenorrhea method

Abbreviation	Expanded Term
LFTs	liver function tests
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MAPK	mitogen-activated protein kinase
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
M&N	Miettinen-Nurminen
MRI	magnetic resonance imaging
mRNA	messenger RNA
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	non–small cell lung cancer
ONJ	osteonecrosis of the jaw
OR	objective response
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PBPK	physiologically based PK
PD	progressive disease
PD-1	programmed cell death 1
PDGFR	platelet-derived growth factor receptor
PD-L1	programmed cell death – ligand 1
PFS	progression-free survival
Pgp	P-glycoprotein
PK	pharmacokinetic
PO	oral(ly)
PopPK	population pharmacokinetic
PR	partial response
PRES/RPLS	posterior reversible encephalopathy syndrome/reversible encephalopathy syndrome/reversible posterior leukoencephalopathy syndrome
PRO	patient reported outcome
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
Q9W	every 9 weeks
Q12W	every 12 weeks
QD	once daily
QoL	quality of life
QTc	corrected QT interval
QTcF	QT interval corrected with Fridericia's formula
R/M	recurrent/metastatic
RBC	red blood cell
RCC	renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RR	response rates
RTKi	receptor tyrosine kinase inhibitor

Abbreviation	Expanded Term
RUQ	right upper quadrant
SAE	serious adverse event
SD	stable disease
SGOT	serum glutamate oxaloacetate transaminase
SGPT	serum glutamate pyruvate transaminase
SIM	Site Imaging Manual
SoA	schedule of activities
SOC	standard of care
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
T3	triiodothyronine
T4	thyroxine
TAM	tumor-associated macrophage
TBL	total bilirubin level
TPS	tumor proportion score
TRAEs	treatment-related adverse events
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
UPCR	urine protein-to-creatinine ratio
USPI	United States Prescribing Information
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of non-childbearing potential

11 REFERENCES

[Aaronson, N. K., et al 1993]	Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365-76.	[03Q3QL]
[Argiris, A., et al 2013]	Argiris A, Ghebremichael M, Gilbert J, Lee J-W, Sachidanandam K, Kolesar JM, et al. Phase III randomized, placebo-controlled trial of docetaxel with or without gefitinib in recurrent or metastatic head and neck cancer: an Eastern Cooperative Oncology Group trial. J Clin Oncol 2013;31(11):1405-14.	[03WNBD]
[Argiris, A., et al 2017]	Argiris A, Harrington KJ, Tahara M, Schulten J, Chomette P, Ferreira Castro A, et al. Evidence-based treatment options in recurrent and/or metastatic squamous cell carcinoma of the head and neck. Front Oncol. 2017 May 9;7:72.	[054MKN]
[Bauml, J., et al 2017]	Bauml J, Seiwert TY, Pfister DG, Worden F, Liu SV, Gilbert J, et al. Pembrolizumab for Platinum- and Cetuximab-Refractory Head and Neck Cancer: Results From a Single-Arm, Phase II Study. J Clin Oncol. 2017 May 10;35(14):1542-1549.	[04QTG6]
[Bjordal, K., et al 1994]	Bjordal K, Ahlner-Elmqvist M, Tollesson E, Jensen AB, Razavi D, Maher EJ, et al. Development of a European Organization for Research and Treatment of Cancer (EORTC) questionnaire module to be used in quality of life assessments in head and neck cancer patients. Acta Oncol 1994;33(8):879-85.	[03WNBB]

[Bjordal, K., et al 2000]	Bjordal K, de Graeff A, Fayers PM, Hammerlid E, van Pottelsberghe C, Curran D, et al. A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. EORTC Quality of Life Group. Eur J Cancer. 2000 Sep;36(14):1796-807.	[040VGM]
[Brose, M., et al 2018]	Brose M, Vogelzang N, Simone CD, Jain S, Richards D, Encarnacion CA, et al. A phase 1b/2 trial of lenvatinib in combination with pembrolizumab in patients with non-small cell lung cancer [abstract]. Presented at: 33rd Annual Meeting & Pre-Conference Programs, Society for Immunotherapy of Cancer (SITC); 2018 Nov 7-11; Washington, DC. Abstract no. P392.	[053BPT]
[Burtness, B., et al 2018]	Burtness B, Harrington KJ, Greil R, Soulieres D, Tahara M, De Castro G Jr, et al. KEYNOTE-048: phase III study of first-line pembrolizumab (P) for recurrent/metastatic head and neck squamous cell carcinoma (R/MHNSCC) [abstract]. Presented at: European Society for Medical Oncology (ESMO) 2018 Congress; 2018 Oct 19-23; Munich (Germany). Ann Oncol. 2018 Oct;29(suppl 8):viii729. Abstract no. LBA8_PR.	[053ZSC]
[Chemnitz, J. M., et al 2004]	Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.	[00VMPN]

[Chow, L. Q., et al 2016]	Chow LQ, Haddad R, Gupta S, Mahipal A, Mehra R, Tahara M, et al. Antitumor Activity of Pembrolizumab in Biomarker-Unselected Patients With Recurrent and/or Metastatic Head and Neck Squamous Cell Carcinoma: Results From the Phase Ib KEYNOTE-012 Expansion Cohort. J Clin Oncol. 2016 Nov 10;34(32):3838-45.	[04M4TX]
[Clopper, C. J. and Pearson, E. S. 1934]	Clopper CJ and Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26(4):404-13.	[03Y75Y]
[Cohen, E. E. W., et al 2018]	Cohen EEW, Soulieres D, Le Tourneau C, Dinis J, Licitra LF, Ahn MJ, et al. Health-related quality of life (HRQoL) of pembrolizumab (pembro) vs standard of care (SOC) for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) in KEYNOTE-040 [abstract]. Presented at: 2018 American Society of Clinical Oncology (ASCO) Annual Meeting; 2018 Jun 1-5; Chicago, IL. J Clin Oncol. 2018;36(15 suppl). Abstract no. 6013.	[052NW6]
[Cohen, E. E. W., et al 2019]	Cohen EEW, Soulieres D, Le Tourneau C, Dinis J, Licitra L, Ahn MJ, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. Lancet. 2019 Jan 12;393:156-67.	[056TMW]
[Colevas, A. D. 2006]	Colevas AD. Chemotherapy options for patients with metastatic or recurrent squamous cell carcinoma of the head and neck. J Clin Oncol. 2006 Jun 10;24(17):2644-52.	[04NZCD]

[Cross, M. J. and Claesson-Welsh L. 2001]	Cross MJ, Claesson-Welsh L. FGF and VEGF function in angiogenesis: signalling pathways, biological responses and therapeutic inhibition. Trends Pharmacol Sci. 2001 Apr;22(4):201-7.	[04XKP6]
[Disis, M. L. 2010]	Disis ML. Immune regulation of cancer. J Clin Oncol 2010;28(29):4531-8.	[058SQL]
[Dorsey, K. 2013]	Dorsey K, Agulnik M. Promising new molecular targeted therapies in head and neck cancer. Drugs. 2013 Mar;73(4):315-25.	[03YXPC]
[Dudley, M. E., et al 2005]	Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.	[00VMPR]
[Ellis, L. M. and Hicklin, D. J. 2008]	Ellis LM, Hicklin DJ. VEGF-targeted therapy: mechanisms of anti-tumour activity. Nat Rev Cancer. 2008 Aug;8:579-91.	[04XKPD]
[Ferrara, N., et al 2003]	Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med. 2003 Jun;9(6):669-76.	[04XKQ2]
[Francisco, L. M., et al 2010]	Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.	[058SQP]
[Fury, M. G., et al 2012]	Fury MG, Sherman E, Lisa D, Agarwal N, Algazy K, Brockstein B, et al. A randomized phase II study of cetuximab every 2 weeks at either 500 or 750 mg/m2 for patients with recurrent or metastatic head and neck squamous cell cancer. J Natl Compr Canc Netw 2012;10(11):1391-8.	[03WN9K]
[Greenwald, R. J., et al 2005]	Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515-48.	[00VMQL]

[Guardiola, E., et al 2004]	Guardiola E, Peyrade F, Chaigneau L, Cupissol D, Tchiknavorian X, Bompas E, et al. Results of a randomised phase II study comparing docetaxel with methotrexate in patients with recurrent head and neck cancer. Eur J Cancer. 2004 Sep;40(14):2071-6.	[045DP4]
[Gupta, B., et al 2016]	Gupta B, Johnson NW, Kumar N. Global Epidemiology of Head and Neck Cancers: A Continuing Challenge. Oncology. 2016;91(1):13-23.	[04P7DZ]
[Harrington, K. J., et al 2017]	Harrington KJ, Ferris RL, Blumenschein G Jr, Colevas AD, Fayette J, Licitra L, et al. Nivolumab versus standard, single-agent therapy of investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck (CheckMate 141): health-related quality-of-life results from a randomised, phase 3 trial. Lancet Oncol. 2017 Aug;18:1104-15.	[052NW7]
[Hitt, R., et al 2006]	Hitt R, Amador ML, Quintela-Fandino M, Jimeno A, del Val O, Hernando S, et al. Weekly docetaxel in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. Cancer 2006;106(1):106-11.	[03WN8P]
[Hunder, N. N., et al 2008]	Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.	[00VMPX]
[IB Edition 16 2019]	Lenvatinib (LENVIMA®, KISPLYX®) Investigator’s Brochure, Edition Number 16, 14-May-2019.	[057WXK]

[Kato, Y., et al 2019]	Kato Y, Tabata K, Kimura T, Yachie-Kinoshita A, Ozawa Y, Yamada K, et al. Lenvatinib plus anti-PD-1 antibody combination treatment activates CD8(+) T cells through reduction of tumor-associated macrophage and activation of the interferon pathway. PLoS One. 2019 Feb 27;14(2):e0212513.	[057JXY]
[Kimura, T., et al 2018]	Kimura T, Kato Y, Ozawa Y, Kodama K, Ito J, Ichikawa K, et al. Immunomodulatory activity of lenvatinib contributes to antitumor activity in the Hepa1-6 hepatocellular carcinoma model. Cancer Sci. 2018;109:3993-4002.	[057LPH]
[Lala, M., et al 2018]	Lala M, Chirovsky D, Cheng JD, Mayawala K. Clinical outcomes with therapies for previously treated recurrent/metastatic head-and-neck squamous cell carcinoma (R/M HNSCC): a systematic literature review. Oral Oncol. 2018;84:108-20.	[05CTJW]
[Licitra, L., et al 2024]	Licitra L, Tahara M, Harrington K, Olivera Hurtado de Mendoza M, Guo Y, Aksoy S, et al. Pembrolizumab with or without lenvatinib as first-line therapy for recurrent or metastatic head and neck squamous cell carcinoma(R/MHNSCC): phase3 LEAP-010 study [abstract]. Presented at: American Society for Radiation Oncology (ASTRO) 2024 Virtual Scientific Abstracts; 2024 Feb 29 - March 02; Arlington, VA. Int J Radiat Oncol Biol Phys. 2024;118(suppl 5):e3.	[08M2JW]
[Lieu, C., et al 2011]	Lieu C, Heymach J, Overman M, Tran H, Kopetz S. Beyond VEGF: inhibition of the fibroblast growth factor pathway and antiangiogenesis. Clin Cancer Res. 2011 Oct 1;17(19):6130-9.	[04XKQM]

[Limaverde-Sousa, G., et al 2014]	Limaverde-Sousa G, Sternberg C, Ferreira CG. Antiangiogenesis beyond VEGF inhibition: a journey from antiangiogenic single-target to broad-spectrum agents. Cancer Treat Rev. 2014;40:548-57.	[04XKQW]
[Machiels, J. P. 2011]	Machiels JP, Schmitz S. Management and palliative chemotherapy for metastatic or recurrent squamous cell carcinoma of the head and neck. Expert Rev Anticancer Ther. 2011;11(3):359-71.	[054PG7]
[Machiels, J. P., et al 2015]	Machiels JP, Haddad RI, Fayette J, Licitra LF, Tahara M, Vermorken JB, et al. Afatinib versus methotrexate as second-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck progressing on or after platinum-based therapy (LUX-Head & Neck 1): an open-label, randomised phase 3 trial. Lancet Oncol. 2015 May;16(5):583-94.	[0488YQ]
[Makker, V., et al 2018]	Makker V, Rasco D, Vogelzang NJ, Messing M, Brose MS, Cohn AL, et al. Lenvatinib + Pembrolizumab in patients with advanced endometrial cancer: updated results. Poster session presented at: 2018 American Society of Clinical Oncology (ASCO) Annual Meeting; 2018 Jun 1-5; Chicago, IL. Poster no. 5596.	[04YJ9J]
[Martinez-Trufero, J., et al 2010]	Martinez-Trufero J, Isla D, Adansa JC, Irigoyen A, Hitt R, Gil-Arnaiz I, et al. Phase II study of capecitabine as palliative treatment for patients with recurrent and metastatic squamous head and neck cancer after previous platinum-based treatment. Br J Cancer. 2010 Jun 8;102(12):1687-91.	[048BMB]

[Mehra, R., et al 2016]	Mehra R, Seiwert TY, Mahipal A, Weiss J, Berger R, Paul Eder J et al. Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC): Pooled analyses after longterm followup in KEYNOTE012 [abstract]. J Clin Oncol. 2016;34(suppl). Abstract no. 6012.	[04GZ3C]
[Merck & Co., Inc. 2023]	Merck Inventing For Life [Internet]. Kenilworth (NJ): Merck & Co., Inc.; c2024. Merck and Eisai provide update on phase 3 LEAP-010 trial evaluating KEYTRUDA® (pembrolizumab) plus LENVIMA® (lenvatinib) in patients with certain types of recurrent or metastatic head and neck squamous cell carcinoma [press release]. 2023 Aug 25 [cited 2024 June 5]; 32 p. Available from: https://www.merck.com/news/merck-and-eisai-provide-update-on-phase-3-leap-010-trial-evaluating-keytruda-pembrolizumab-plus-lenvima-lenvatinib-in-patients-with-certain-types-of-recurrent-or-metastatic-head-and-ne/.	[08LK94]
[Mesia, R., et al 2010]	Mesia R, Rivera F, Kawecki A, Rottey S, Hitt R, Kienzer H, et al. Quality of life of patients receiving platinum-based chemotherapy plus cetuximab first line for recurrent and/or metastatic squamous cell carcinoma of the head and neck. Ann Oncol. 2010 Oct;21(10):1967-73.	[040WNJ]
[Miettinen, O. and Nurminen, M. 1985]	Miettinen O and Nurminen M. Comparative analysis of two rates. Stat Med 1985;4:213-26.	[00VMQY]
[National Comprehensive Cancer Network 2018]	National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: head and neck cancers; version 1.2018. Fort Washington (PA): National Comprehensive Cancer Network (NCCN); 2018. 218 p.	[04YNJY]

[Okazaki, T., et al 2001]	Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98(24):13866-71.	[00VMQ6]
[Parry, R. V., et al 2005]	Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 2005;25(21):9543-53.	[00VMQ7]
[Pennock, G. K. 2015]	Pennock GK, Chow LQM. The evolving role of immune checkpoint inhibitors in cancer treatment. Oncologist. 2015;20:812-22.	[04XQM6]
[Pickard, A. S., et al 2007]	Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes 2007;5:1-8.	[00W0FM]
[Pickard, A. S., et al 2007a]	Pickard AS, Wilke CT, Lin H-W, Lloyd A. Health utilities using the EQ-5D in studies of cancer. Pharmacoeconomics 2007;25(5):365-84.	[03RLHG]
[Price, K. A. 2012]	Price KA, Cohen EE. Current treatment options for metastatic head and neck cancer. Curr Treat Options Oncol. 2012 Mar;13(1):35-46.	[03YXPS]
[Rabin, R. and de Charro, F. 2001]	Rabin R and de Charro F. EQ-5D: a measure of health status from the EuroQol group. Ann Med 2001;33:337-43.	[03QM46]
[Riley, J. L. 2009]	Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.	[00VMQ9]
[Sacco, A. G. 2015]	Sacco AG, Cohen EE. Current Treatment Options for Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma. J Clin Oncol. 2015 Oct 10;33(29):3305-13.	[04NZCY]

[Sheppard, K-A, et al 2004]	Sheppard K-A, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 2004;574:37-41.	[00VMQC]
[Soulieres, D., et al 2017]	Soulieres D, Faivre S, Mesia R, Remenar E, Li SH, Karpenko A, et al. Buparlisib and paclitaxel in patients with platinum-pretreated recurrent or metastatic squamous cell carcinoma of the head and neck (BERIL-1): a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Oncol. 2017 Mar;18:323-35.	[05FX2F]
[Tammela, T. and Alitalo, K. 2010]	Tammela T, Alitalo K. Lymphangiogenesis: molecular mechanisms and future promise. Cell. 2010 Feb 19;140:460-76.	[04XKRB]
[Taylor, M. H., et al 2018]	Taylor MH, Rasco DW, Brose MS, Vogelzang NJ, Richey SL, Cohn AL, et al. A phase 1b/2 trial of lenvatinib plus pembrolizumab in patients with squamous cell carcinoma of the head and neck. Poster session presented at: 2018 American Society of Clinical Oncology (ASCO) Annual Meeting; 2018 Jun 1-5; Chicago, IL. Poster no. 6016.	[053L8W]
[Taylor, M. H., et al 2018a]	Taylor MH, Rasco DW, Brose MS, Vogelzang NJ, Richey SL, Richards DA, et al. A phase 1b/2 trial of lenvatinib plus pembrolizumab in patients with squamous cell carcinoma of the head and neck [abstract]. Presented at: 2018 American Society of Clinical Oncology (ASCO) Annual Meeting; 2018 Jun 1-5; Chicago, IL. J Clin Oncol. 2018;36(15 suppl). Abstract no. 6016.	[053BZJ]

[Taylor, M. H., et al 2020]	Taylor MH, Lee CH, Makker V, Rasco D, Dutcus CE, Wu J, et al. Phase IB/II trial of lenvatinib plus pembrolizumab in patients with advanced renal cell carcinoma, endometrial cancer, and other selected advanced solid tumors. J Clin Oncol. In press 2020.	[05GF7R]
[Taylor, M., et al 2018]	Taylor M, Vogelzang N, Cohn A, Stepan D, Shumaker R, Dutcus C, et al. A phase 1b/2 trial of lenvatinib in combination with pembrolizumab in patients with advanced melanoma [abstract]. Presented at: 33rd Annual Meeting & Pre-Conference Programs, Society for Immunotherapy of Cancer (SITC); 2018 Nov 7-11; Washington, DC. Abstract no. P391.	[053BQ3]
[U.S. Prescribing Information 2017]	U.S. Prescribing Information: PACLITAXEL- paclitaxel injection, solution: Oct 2017.	[05FYK5]
[U.S. Prescribing Information 2018]	U.S. Prescribing Information: KEYTRUDA (pembrolizumab) for injection, for intravenous use; KEYTRUDA (pembrolizumab) injection, for intravenous use: Nov 2018.	[053BHH]
[U.S. Prescribing Information 2018a]	U.S. Prescribing Information: LENVIMA (lenvatinib) capsules, for oral use: Jun 2018.	[04YSFP]
[Vermorken, J. B. 2010]	Vermorken JB, Specenier P. Optimal treatment for recurrent/metastatic head and neck cancer. Ann Oncol. 2010 Oct;21 Suppl 7:vii252-61.	[04N54Z]
[Vermorken, J. B., et al 2007]	Vermorken JB, Trigo J, Hitt R, Koralewski P, Diaz-Rubio E, Rolland F, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. J Clin Oncol 2007;25(16):2171-7.	[03WNB5]

[Vermorken, J. B., et al 2008]	Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116-27.	[03WNBF]
[Vigneswaran, N. 2014]	Vigneswaran N, Williams MD. Epidemiological trends in head and neck cancer and aids in diagnosis [manuscript]. Oral Maxillofac Surg Clin North Am. 2014. 35 p.	[05D0DJ]
[Vogelzang, N., et al 2018]	Vogelzang N, Encarnacion C, Cohn A, Simone CD, Rasco D, Richards D, et al. A phase 1b/2 trial of lenvatinib in combination with pembrolizumab in patients with urothelial cancer [abstract]. Presented at: 33rd Annual Meeting & Pre-Conference Programs, Society for Immunotherapy of Cancer (SITC); 2018 Nov 7-11; Washington, DC. Abstract no. P393.	[053BQ4]
[Yamamoto, Y., et al 2014]	Yamamoto Y, Matsui J, Matsushima T, Obaishi H, Miyazaki K, Nakamura K, et al. Lenvatinib, an angiogenesis inhibitor targeting VEGFR/FGFR, shows broad antitumor activity in human tumor xenograft models associated with microvessel density and pericyte coverage. Vasc Cell. 2014;6:18.	[04XQ0S]
[Zhang, X., et al 2004]	Zhang X, Schwartz J-CD, Guo X, Bhatia S, Cao E, Chen L, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47.	[00VMQJ]