Official Protocol Title:	A Phase III, Randomized, Open-label Study to Evaluate Pembrolizumab as Neoadjuvant Therapy and in Combination With Standard of Care as Adjuvant Therapy for Stage III-IVA Resectable Locoregionally Advanced Head and Neck Squamous Cell Carcinoma (LA HNSCC)
NCT number:	NCT03765918
Document Date:	29-Mar-2024

TITLE PAGE

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Protocol Title: A Phase III, Randomized, Open-label Study to Evaluate Pembrolizumab as Neoadjuvant Therapy and in Combination With Standard of Care as Adjuvant Therapy for Stage III-IVA Resectable Locoregionally Advanced Head and Neck Squamous Cell Carcinoma (LA HNSCC)

Protocol Number: 689-09

Compound Number: MK-3475

Sponsor Name and Legal Registered Address:

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

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

Regulatory Agency Identifying Number(s):

IND NUMBER: 122,325

EudraCT NUMBER: 2017-001139-38

EU CT NUMBER: 2022-500254-41-00

jRCT NUMBER: 2080224953

Approval Date: 29 March 2024

Sponsor Signatory

Typed Name:
Title:

Date

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

Investigator Signatory

I agree to conduct this clinical trial 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
3475-689-09	29-MAR-2024	To update the assumptions of the survival distribution of the control arm [redacted]
3475-689-08	07-SEP-2023	To amend the statistical analysis plan, [redacted]
3475-689-07	07-JUN-2022	To update contraception language to include required duration of contraception for males and women of childbearing potential (WOCBP) after radiotherapy (RT). Additional minor updates, corrections, and clarifications were also made.
3475-689-06	03-MAR-2022	1) To add pregnancy testing for women of childbearing potential (WOCBP) at monthly intervals during study treatment until 120 days after the last dose of pembrolizumab and 180 days after the last dose of cisplatin, including at the end of treatment visit. 2) To allow imaging and/or biopsy assessments to continue for participants who have not experienced an event. 3) To update the contraception requirements and make additional minor corrections and clarifications throughout the protocol.
3475-689-05	13-MAY-2021	To update the dose modification and toxicity management guidelines for immune-related adverse events (irAEs).

Document	Date of Issue	Overall Rationale
3475-689-04	17-JUN-2019	To add both biomarker-driven hypotheses and the stratification factor of tumor proportion score (TPS) ≥ 50%. CCI [redacted]
3475-689-03	02-AUG-2018	To clarify the definitions of residual disease used in the pathological assessment used for this study and to clarify the roles of the local and central pathologists, to align the pembrolizumab dose modification table with the most current safety information, and to remove iRECIST assessment which is not relevant for this study. Additional clarifications and corrections were also made.
3475-689-02	10-MAY-2018	To align with regulatory requirements at German and French sites as well as to align with the cisplatin SmPC as required for German and French sites.
3475-689-01	13-JAN-2018	To provide for more frequent pregnancy testing and to extend the prohibition of live vaccines to 3 months after the end of study treatment.
3475-689-00	24-AUG-2017	Initial protocol

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 09

Overall Rationale for the Amendment: To update the assumptions of the survival distribution of the control arm based on historical data and update with more conservative HR assumption for EFS in CPS≥10 population based on study data from KEYNOTE-412.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 10.1, Statistical Analysis Plan Summary	To update the assumptions of the survival distribution of the control arm [redacted]	Changes made were to address strategy. [redacted]
Additional Changes		
Section 1, Synopsis	Number of Participants: Updated planned sample sizes in CPS≥10, CPS≥1, and ITT populations.	To reflect the actual enrollment in CPS≥10, CPS≥1, and ITT populations.
Section 5.1, Overall Design	Updated planned sample sizes in CPS≥10, CPS≥1, and ITT populations.	Refer to the rationale provided for Section 1 above regarding the number of participants enrolled.
Section 5.2, Number of Participants	Updated planned sample sizes in CPS≥10, CPS≥1, and ITT populations.	Refer to the rationale provided for Section 1 above regarding the number of participants enrolled.
Section 10.1, Statistical Analysis Plan Summary	Treatment Assignment: Updated planned sample sizes in CPS≥10, CPS≥1, and ITT populations.	Refer to the rationale provided for Section 1 above regarding the number of participants enrolled.
Section 10.1, Statistical Analysis Plan Summary	Interim Analyses: Added clarification that [redacted]	Updated the [redacted]
Section 10.1, Statistical Analysis Plan Summary	Sample Size and Power: Updated planned sample sizes in CPS≥10, CPS≥1, and ITT populations.	Refer to the rationale provided for Section 1 above regarding the number of participants enrolled.
Section 10.1, Statistical Analysis Plan Summary	Sample Size and Power: Removed specification that the final analysis of the study is event driven.	This statement is not applicable in sample size and power section.

Section Number and Name	Description of Change	Brief Rationale
Section 10.7.1, Efficacy Interim Analysis	Table 16: Updated the timing for interim and final analyses.	Refer to the rationale provided for Section 10.1 above regarding CCI [redacted]
Section 10.7.1, Efficacy Interim Analysis	Table 16: Added clarification that CCI [redacted]	Refer to the rationale provided for Section 10.1 above regarding CCI [redacted]
Section 10.8.1.1, Event-Free Survival	Updated CCI [redacted].	Refer to the rationale provided for Section 10.1 above regarding CCI [redacted]
Section 10.8.1.1, Event-Free Survival	Table 18: Updated CCI [redacted]	Refer to the rationale provided for Section 10.1 above CCI [redacted].
Section 10.8.1.1, Event-Free Survival	Updated CCI [redacted]	Refer to the rationale provided for Section 10.1 above CCI [redacted].
Section 10.8.1.1, Event-Free Survival	Table 19: Updated CCI [redacted]	Refer to the rationale provided for Section 10.1 above regarding CCI [redacted]
Section 10.8.1.1, Event-Free Survival	Table 20: Updated CCI [redacted]	Refer to the rationale provided for Section 10.1 above regarding CCI [redacted].
Section 10.8.1.2, Major Pathologic Response	Table 21: Updated CCI [redacted]	CCI [redacted]
Section 10.8.1.3, Overall Survival	Updated CCI [redacted]	Refer to the rationale provided for Section 10.1 above CCI [redacted].
Section 10.8.1.3, Overall Survival	Table 22: Updated CCI [redacted]	Refer to the rationale provided for Section 10.1 above CCI [redacted].
Section 10.8.1.3, Overall Survival	Table 23: Updated CCI [redacted]	Refer to the rationale provided for Section 10.1 above CCI [redacted].

Section Number and Name	Description of Change	Brief Rationale
Section 10.8.1.3, Overall Survival	Table 24: Updated CCI [redacted].	Refer to the rationale provided for Section 10.1 above regarding CCI [redacted]
Section 10.9, Sample Size and Power Calculations	CCI [redacted]	Refer to the rationale provided for Section 10.1 above regarding CCI [redacted]
Section 10.9, Sample Size and Power Calculations		Refer to the rationale provided for Section 10.1 above regarding CCI [redacted]
Section 10.9, Sample Size and Power Calculations		Refer to the rationale provided for Section 10.1 above regarding CCI [redacted]
Section 10.9, Sample Size and Power Calculations		Refer to the rationale provided for Section 10.8.1.2 above CCI [redacted]
Section 10.10, Subgroup Analyses	Removed stratification factors from subgroup analyses.	Primary tumor site, tumor stage, and PD-L1 status will be based on eCRF data.
Appendix 3: Regulatory, Ethical, and Study Governance Considerations	Added clarification that records and documents under EU CTR regulation must be retained for 25 years after the end of the study.	Refer to the rationale provided for Appendix 3 above regarding compliance with Regulation (EU) 536/2014.
Appendix 3: Regulatory, Ethical, and Study Governance Considerations	Added statement that the clinical trial will be conducted in compliance with Regulation (EU) 536/2014.	This change was made to comply with Regulation (EU) 536/2014.
Appendix 3: Regulatory, Ethical, and Study Governance Considerations	Added serious breach reporting requirements.	Refer to the rationale provided for Appendix 3 above regarding compliance with Regulation (EU) 536/2014.
Throughout document	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 SYNOPSIS

Protocol Title: A Phase III, Randomized, Open-label Study to Evaluate Pembrolizumab as Neoadjuvant Therapy and in Combination With Standard of Care as Adjuvant Therapy for Stage III-IVA Resectable Locoregionally Advanced Head and Neck Squamous Cell Carcinoma (LA HNSCC)
Short Title: MK-3475 (SCH 9000475) as neoadjuvant and adjuvant therapy in Stage III-IVA resectable LA HNSCC
Objectives/Hypotheses and Endpoints: All objectives and hypotheses apply to male/female adult participants (≥18 years of age) with resectable locoregionally advanced head and neck squamous cell carcinoma (LA HNSCC). 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 5.4.1.1.3 for further details.

Objective/Hypothesis	Endpoint
Primary	
• Objective 1: To compare pembrolizumab as neoadjuvant therapy and in combination with radiotherapy (RT) ± cisplatin as adjuvant therapy to only RT ± cisplatin as adjuvant therapy with respect to the event-free survival (EFS), per RECIST 1.1, as assessed by blinded independent central review (BICR) in participants whose tumors express PD-L1 CPS≥10, CPS≥1, and in all participants, regardless of CPS status. - Hypothesis #1: Pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy after surgical resection is superior to standard of care (SoC) surgical resection followed by RT ± cisplatin adjuvant therapy with respect to EFS, per RECIST 1.1, by BICR in participants whose tumors express PD-L1 CPS≥10. - Hypothesis #2: Pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy after surgical resection is superior to standard of care (SoC) surgical resection followed by RT ± cisplatin adjuvant therapy with respect to EFS, per RECIST 1.1, by BICR in participants whose tumors express PD-L1 CPS≥1. - Hypothesis #3: Pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy after surgical resection is superior to standard of care (SoC) surgical resection followed by RT ± cisplatin adjuvant therapy with respect to EFS, per RECIST 1.1, by BICR in all participants.	• EFS –time from the date of randomization to the date of first record of any of the following events: radiographic disease progression (exceptions specified in Section 10.4.1.1), radiographic disease progression during the neoadjuvant phase that precludes surgery, local or distant disease progression or recurrence, as assessed with imaging or biopsy as indicated, death due to any cause; a secondary primary malignancy is not considered an EFS event

Secondary	
• Objective 2: To compare pembrolizumab neoadjuvant therapy to no neoadjuvant therapy with respect to the rate of major pathological response (mPR) as assessed by the central pathologist at the time of definitive surgery in participants whose tumors express PD-L1 CPS≥10, CPS≥1, and in all participants regardless of CPS status. - Hypothesis #4: Pembrolizumab neoadjuvant therapy is superior to no neoadjuvant therapy with respect to rate of mPR at the time of surgery in participants whose tumors express PD-L1 CPS≥10. - Hypothesis #5: Pembrolizumab neoadjuvant therapy is superior to no neoadjuvant therapy with respect to rate of mPR at the time of surgery in participants whose tumors express PD-L1 CPS≥1. - Hypothesis #6: Pembrolizumab neoadjuvant therapy is superior to no neoadjuvant therapy with respect to rate of mPR at the time of surgery in all participants.	• mPR – having less than or equal to 10% invasive squamous cell carcinoma within the resected primary tumor specimen and all sampled regional lymph nodes

• Objective 3: To compare pembrolizumab as neoadjuvant therapy and in combination with radiotherapy (RT) ± cisplatin as adjuvant therapy to only RT ± cisplatin as adjuvant therapy with respect to overall survival (OS) in participants whose tumors express PD-L1 CPS≥10, CPS≥1, and in all participants, regardless of CPS status. - Hypothesis #7: Pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy after surgical resection is superior to SoC surgical resection followed by RT ± cisplatin adjuvant therapy with respect to OS in participants whose tumors express PD-L1 CPS≥10. - Hypothesis #8: Pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy after surgical resection is superior to SoC surgical resection followed by RT ± cisplatin adjuvant therapy with respect to OS in participants whose tumors express PD-L1 CPS≥1. - Hypothesis #9: Pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy after surgical resection is superior to SoC surgical resection followed by RT ± cisplatin adjuvant therapy with respect to OS in all participants.	• OS - time from the date of randomization to the date of death due to any cause
• Objective 4: To evaluate the rate of pathological complete response (pCR), as assessed by the central pathologist at the time of definitive surgery, in participants whose tumors express PD-L1 CPS≥10, CPS≥1, and in all participants regardless of CPS status.	• pCR - having no residual invasive squamous cell carcinoma within the resected primary tumor specimen and all sampled regional lymph nodes

• Objective 5: To evaluate global health status/quality of life (QoL) and physical functioning scores using the European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire (QLQ)-C30, and swallowing, speech and pain symptoms using the EORTC Head and Neck–Specific QoL questionnaire (EORTC QLQ-H&N35) in participants whose tumors express PD-L1 CPS≥10, CPS≥1, and in all participants, regardless of CPS status.	• EORTC QLQ C30 global health status/QoL scales (items 29 and 30) • EORTC QLQ-C30 physical functioning scales (items 1-5) • EORTC QLQ-H&N35 swallowing multi-item scale (items 35-38), speech multi-item scale (items 46, 53-54), and pain multi-item scale (items 31-34)
• Objective 6: To determine the safety and tolerability of pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy.	• Adverse events (AEs) • Study drug discontinuations due to AEs

The study is considered to have met its objective if pembrolizumab is superior to SoC with respect to EFS at either its interim analysis (IA) or the final analysis.

Overall Design:

Study Phase	Phase III
Clinical Indication	The treatment of participants with Stage III-IVA, resectable, locoregionally advanced head and neck squamous cell carcinoma (LA HNSCC)
Population	Treatment naïve participants with Stage III-IVA resectable LA HNSCC
Study Type	Interventional
Type of Design	Randomized, open-label
Type of Control	Active control no placebo
Study Blinding	Unblinded Open-label
Estimated Duration of Trial	The Sponsor estimates that the trial will require approximately 7 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:

The number of participants planned to be enrolled in the study was 704. The actual number of participants enrolled in the study will be 714 participants, which will result in approximately 65% (~462) participants whose tumors express PD-L1 CPS≥10 and approximately 95% (~680) participants whose tumors express PD-L1 CPS≥1.

Treatment Groups and Duration:

Treatment Groups	There are 2 treatment arms: • Treatment Arm A/pembrolizumab: Neoadjuvant therapy: pembrolizumab (2 cycles) prior to surgical resection. Adjuvant therapy: Pembrolizumab (15 cycles) plus SoC RT with/without cisplatin. • Treatment Arm B/SoC: Neoadjuvant therapy: no treatment prior to surgical resection. Adjuvant: SoC RT with/without cisplatin. Pembrolizumab: 200 mg fixed dose, intravenously (IV) every 3 weeks (Q3W), in the neoadjuvant and adjuvant treatment periods. No crossover from SoC to pembrolizumab will be permitted.
Duration of Participation	Each participant will participate in the study from the time that the participant provides documented informed consent through the final protocol-specified contact. After a screening phase of 28 days, eligible participants will be stratified and randomly assigned to receive study treatment until an event/disease progression is radiographically documented and verified by BICR, unacceptable AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, withdrawal of consent, or administrative reasons requiring cessation of treatment, or until the participant has received 17 administrations of pembrolizumab (approximately 1 year). After the end of treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 9.3. Participants who discontinue for reasons other than an event/disease progression/recurrence will have post treatment follow-up imaging for disease status until an event/disease progression/recurrence as per Section 10.4.1.1, withdrawing consent, or becoming lost to follow-up. All participants will be followed by telephone for OS until death, withdrawal of consent, or the end of the study.

A list of abbreviations used in this document can be found in Appendix 1. Study governance considerations are outlined in Appendix 3.

2 SCHEDULE OF ACTIVITIES (SOA)

2.1 Study Screening and Treatment 1 Phases (Arm A/Pembrolizumab)

Study Screening and Treatment 1 Phases (Arm A/Pembrolizumab)								
Study Period	**Screening**	**Treatment randomization**	**Treatment 1**		**Presurgery Imaging/ Safety[c]**	**Surgery[c]**	**Post-surgery Safety Follow-up**	**Notes:** Participants that discontinue study treatment for reasons other than an event/disease progression will enter post-treatment study follow-up. Participants who discontinue study treatment due to an event/disease progression will enter Safety and Survival Follow-up.
Visit Number/Title			**Pembro neoadjuvant**					
Treatment Cycle			**1**	**2**				
Week			**1**	**4**	**6**			
Scheduled Day (s)			**1**	**1**	**1**			
Scheduling Window (Days, unless noted)	**-28 to -1**		**+3**	**±3**	**±10**		**7-30 days post-surgery**	
Administrative Procedures								
Informed Consent	X							Documented informed consent must be obtained prior to performing any protocol-specified procedures. Results of a test performed prior to the participant providing documented informed consent as part of routine clinical management are acceptable in lieu of a screening test, if performed within the specified time frame. If the investigator plans to treat beyond the initial radiologic disease progression per RECIST 1.1, additional consent will be required prior to post-progression treatment (see Section 9.1.1.1).
Informed Consent for Future Biomedical Research (FBR; optional)	X							
Participant Identification Card	X	X						Distribute at screening and add the randomization number at the time of randomization.
Inclusion/Exclusion Criteria	X							
Demographics, Disease Details and Complete Medical History (includes substance usage)	X							Substances: alcohol and tobacco.

Study Screening and Treatment 1 Phases (Arm A/Pembrolizumab)								
Study Period	**Screening**	**Treatment randomization**	**Treatment 1**		**Presurgery Imaging/ Safety[c]**	**Surgery[c]**	**Post-surgery Safety Follow-up**	**Notes:** Participants that discontinue study treatment for reasons other than an event/disease progression will enter post-treatment study follow-up. Participants who discontinue study treatment due to an event/disease progression will enter Safety and Survival Follow-up.
Visit Number/Title			**Pembro neoadjuvant**					
Treatment Cycle			**1**	**2**				
Week			**1**	**4**	**6**			
Scheduled Day (s)			**1**	**1**	**1**			
Scheduling Window (Days, unless noted)	**-28 to -1**		**+3**	**±3**	**±10**		**7-30 days post-surgery**	
Prior/Concomitant Medication Review	X		X	X	X		X	Prior medications – Record all medications taken within 28 days of randomization. Concomitant medications – Enter new medications started during the study through the post-treatment Safety Follow-up.
Treatment Randomization via IVRS		X						Site personnel will access the IVRS after screening and determining if the participant is eligible for randomization. Sites will contact participants and advise of the assigned treatment arm and date of first visit.
Pembrolizumab Administration			X	X				Treatment 1, Cycle 1 must be given within 3 days of treatment randomization via IVRS. Pembrolizumab to be administered on Day 1 of each cycle after all procedures/ assessments have been completed.
Surgery						X		Performed as part of planned SoC after presurgery imaging. Participants who do not undergo surgery as originally planned, for reasons other than centrally verified radiographic disease progression, may proceed directly to Treatment 2 and receive salvage RT plus cisplatin plus pembrolizumab.

Study Screening and Treatment 1 Phases (Arm A/Pembrolizumab)								
Study Period	**Screening**	**Treatment randomization**	**Treatment 1**		**Presurgery Imaging/ Safety[c]**	**Surgery[c]**	**Post-surgery Safety Follow-up**	**Notes:** Participants that discontinue study treatment for reasons other than an event/disease progression will enter post-treatment study follow-up. Participants who discontinue study treatment due to an event/disease progression will enter Safety and Survival Follow-up.
Visit Number/Title			**Pembro neoadjuvant**					
Treatment Cycle			**1**	**2**				
Week			**1**	**4**	**6**			
Scheduled Day (s)			**1**	**1**	**1**			
Scheduling Window (Days, unless noted)	**-28 to -1**		**+3**	**±3**	**±10**		**7-30 days post-surgery**	
Efficacy Procedures								
CT/MRI head and neck, chest, upper abdomen	X				X*		(X) optional at site discretion	If the participant had received CT/MRI scan prior to providing documented informed consent and within 28 days prior to randomization, the assessment can be accepted. For each participant, the same modality should be used throughout the study for response evaluation. The upper abdominal CT/MRI should cover the liver in its entirety. *Presurgery scans are required within 14 days prior to the date of surgery. Repeat imaging is required if imaging is done >14 days prior to the date of surgery.
FDG-PET or FDG-PET/CT	X							If the participant had received FDG-PET or FDG-PET/CT scan prior to providing documented informed consent and within 28 days prior to randomization, the assessment can be accepted.
Tissue Collection for Histopathology (mPR and pCR assessment)						X		Assessment of surgical margins / gross lesions will be performed by the local pathologist.

Study Screening and Treatment 1 Phases (Arm A/Pembrolizumab)								
Study Period	**Screening**	**Treatment randomization**	**Treatment 1**		**Presurgery Imaging/ Safety[c]**	**Surgery[c]**	**Post-surgery Safety Follow-up**	**Notes:** Participants that discontinue study treatment for reasons other than an event/disease progression will enter post-treatment study follow-up. Participants who discontinue study treatment due to an event/disease progression will enter Safety and Survival Follow-up.
Visit Number/Title			**Pembro neoadjuvant**					
Treatment Cycle			**1**	**2**				
Week			**1**	**4**	**6**			
Scheduled Day (s)			**1**	**1**	**1**			
Scheduling Window (Days, unless noted)	**-28 to -1**		**+3**	**±3**	**±10**		**7-30 days post-surgery**	
Patient Reported Outcomes								
EQ-5D-5L			X	X	X			PROs are to be administered by trained site personnel. It is strongly recommended that PROs are completed by participants prior to all procedures/assessments, and in the following order: EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-H&N35. If the participant does not complete the PROs for any reason, the Miss Mode form must be completed to capture the reason the assessment was not performed.
EORTC QLQ-C30			X	X	X			
EORTC QLQ-H&N35			X	X	X			
Safety Procedures								
Full physical examination including neurological exam and Height*	X						X	To be performed by the investigator or qualified designee. Documented routine neurological exams performed within 6 weeks of randomization are acceptable and do not need to be repeated in Screening. *Height will be measured at Screening only.
Directed physical examination			X	X	X			
ECOG Performance Status	X		X	X	X		X	Screening (within 10 days prior to randomization). Investigator or designee to confirm no deterioration prior to initiating study treatment. ECOG performance status must be 0 or 1 on the first day of dosing. To be assessed prior to dosing.
Weight and Vital Signs	X		X	X	X		X	Vital signs to be collected include: temperature, resting pulse, resting respiratory rate, blood pressure.

Study Screening and Treatment 1 Phases (Arm A/Pembrolizumab)								
Study Period	**Screening**	**Treatment randomization**	**Treatment 1**		**Presurgery Imaging/ Safety[c]**	**Surgery[c]**	**Post-surgery Safety Follow-up**	**Notes:** Participants that discontinue study treatment for reasons other than an event/disease progression will enter post-treatment study follow-up. Participants who discontinue study treatment due to an event/disease progression will enter Safety and Survival Follow-up.
Visit Number/Title			**Pembro neoadjuvant**					
Treatment Cycle			**1**	**2**				
Week			**1**	**4**	**6**			
Scheduled Day (s)			**1**	**1**	**1**			
Scheduling Window (Days, unless noted)	**-28 to -1**		**+3**	**±3**	**±10**		**7-30 days post-surgery**	
12-lead ECG (local)	X							
Urine or Serum β-hCG Pregnancy Test (WOCBP only) – as per local SOP	X		X	(x)			(x)	The protocol requires pregnancy testing at Screening and within 24 hours (urine) or within 72 hours (serum) before randomization. (x) = a pregnancy test must be performed every month during study treatment. More frequent pregnancy testing may be performed if required by local regulations or if determined necessary by the investigator (refer to Appendix 8 for UK-, Germany- and France-specific requirements).
HIV, hepatitis B and C screen (testing optional per site SOP)	X							HIV, hepatitis B and C testing are required when mandated by local health authority. Refer to Appendix 8 for Germany-specific requirements for HIV, Hepatitis B and C testing requirements.
Hematology	X		X	X	X		X	Screening. Labs performed within 10 days of treatment initiation during screening, do not need to be repeated at Treatment 1: Cycle 1, Day 1 unless clinically indicated. Samples to be taken prior to pembrolizumab administration. After Cycle 1 lab samples can be collected up to 3 days prior to the scheduled time point.
Chemistry	X		X	X	X		X	

Study Screening and Treatment 1 Phases (Arm A/Pembrolizumab)								
Study Period	**Screening**	**Treatment randomization**	**Treatment 1**		**Presurgery Imaging/ Safety[c]**	**Surgery[c]**	**Post-surgery Safety Follow-up**	**Notes:** Participants that discontinue study treatment for reasons other than an event/disease progression will enter post-treatment study follow-up. Participants who discontinue study treatment due to an event/disease progression will enter Safety and Survival Follow-up.
Visit Number/Title			**Pembro neoadjuvant**					
Treatment Cycle			**1**	**2**				
Week			**1**	**4**	**6**			
Scheduled Day (s)			**1**	**1**	**1**			
Scheduling Window (Days, unless noted)	**-28 to -1**		**+3**	**±3**	**±10**		**7-30 days post-surgery**	
Urinalysis	X		X	X	X		X	Screening. Labs performed within 10 days of treatment initiation during screening, do not need to be repeated at Treatment 1: Cycle 1, Day 1 unless clinically indicated. Samples to be taken prior to pembrolizumab administration, after Cycle 1, lab samples can be collected up to 3 days prior to the scheduled time point.
Coagulation tests (PT/INR and aPTT/PTT)	X		------If Clinically Indicated------				--If Clinically Indicated--	Any participant receiving anticoagulant therapy should have coagulation tests monitored closely throughout the study. PTT may be performed if the local lab is unable to perform aPTT.
Thyroid Function (TSH)	X			X	---If Clinically Indicated---		--If Clinically Indicated--	In case of elevated TSH, to add Free T3 and Free T4. Free T4 should be performed on all participants with elevated TSH; Free T3 only needs to be performed if it is done as a part of local SOC. If the Free T3 and Free T4 are not available locally, they can be sent to the central laboratory to be performed (see Laboratory Manual for details).
AE/SAE review	X		---Continuous Reporting---					
Oral and dental check-up	X							Recommended every 6 months throughout the study (frequency as per SoC/local guidelines).
Audiometric Testing	X							Documented routine exams performed within 6 weeks of randomization are acceptable and do not need to be repeated in Screening.
Fiber optic examination of primary tumor site	X		--If Clinically Indicated--					

Study Screening and Treatment 1 Phases (Arm A/Pembrolizumab)								
Study Period	**Screening**	**Treatment randomization**	**Treatment 1**		**Presurgery Imaging/ Safety[c]**	**Surgery[c]**	**Post-surgery Safety Follow-up**	**Notes:** Participants that discontinue study treatment for reasons other than an event/disease progression will enter post-treatment study follow-up. Participants who discontinue study treatment due to an event/disease progression will enter Safety and Survival Follow-up.
Visit Number/Title			**Pembro neoadjuvant**					
Treatment Cycle			**1**	**2**				
Week			**1**	**4**	**6**			
Scheduled Day (s)			**1**	**1**	**1**			
Scheduling Window (Days, unless noted)	**-28 to -1**		**+3**	**±3**	**±10**		**7-30 days post-surgery**	
Future Biomedical Research/Biomarkers								
Blood for Genetic Analysis [a]			X					Drawn pre-dose.
Blood for RNA Analysis			X	X				Whole blood samples should be collected pre-dose on Cycle 1 Day 1. Leftover specimens will be stored for FBR if the participant consents to FBR.
Blood for Plasma Biomarker Analyses			X	X				
Blood for Serum Biomarker Analyses			X	X				
Blood for ctDNA			X	X	X			
Tumor Tissue Sample Collection								
Histology, including PD-L1 and p16 biomarker analysis on all participants prior to randomization for stratification, [b]	X							Tumor tissue from core or excisional biopsy (FNA not adequate) from all participants. Results of PD-L1 testing are required for stratification; p16 testing required only for participants with oropharyngeal cancer. PD-L1 (tested centrally) and p16 biomarker analysis (tested locally/centrally).
Tissue Collection for Biomarker Analysis [b]	X					X*		Core or excisional biopsy (FNA not adequate). *For participants who do not achieve a pCR, a tumor tissue sample is to be collected and submitted to the designated central laboratory for translational research.

Refer to Appendix 8 for country-specific requirements.

[a] This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for Future Biomedical Research (FBR) if the participant (or their legally acceptable representative) provides documented informed consent for FBR. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

[b] Baseline tumor tissue from a core or excisional biopsy (FNA not adequate) from participants with oropharyngeal cancer must be tested locally for HPV status (if HPV status not known) prior to randomization. If local p16 testing results are not available, or cannot be assessed locally by the specified method, a tumor tissue sample must be submitted for p16 testing at the designated central laboratory. For all participants, baseline tumor tissue must also be provided to the central vendor for PD-L1 biomarker testing (results required prior to randomization) and translational research. Refer to Section 9.2.2 for additional information about tissue requirements. Detailed instructions for tissue collection, process and shipment are provided in the Vendor Manual. If the participant provides documented informed consent for FBR, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR. Newly obtained biopsies are permitted.

[c] The timeframe for surgery (after the presurgery visit) is 6 weeks (±10 days) after randomization. Participants in Arm A are allowed to go to surgery outside of this timeframe if delays are due to an AE. Participants with delays other than for an AE may be considered with sponsor consultation.

2.2 Post-surgery Treatment 2 Phase (Arm A/Pembrolizumab)

Post-surgery Treatment 2 Phase (Arm A/Pembrolizumab)													
Study Period	**Treatment 2 (adjuvant)**												**Notes** Participants that discontinue study treatment for reasons other than an event/disease progression will enter post-treatment study follow-up. Participants who discontinue study treatment due to an event/disease progression will enter Safety and Survival Follow-up. Upon completion of Treatment 2, participants move into post-treatment follow-up.
Visit Number/Title													
Treatment Cycle	**1**			**2**			**3**	**4**	**5**	**6**	**7**	**8-15**	
Week	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**10**	**13**	**16**	**19**	**22-43**	
Scheduled Day(s)	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**	**1**	**1**	**1**	
Scheduling Window (Days, unless noted)	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Administrative Procedures													
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	
Pembrolizumab Administration	X			X			X	X	X	X	X	X	To be administered after all procedures/assessments have been completed. If the start of RT is delayed, up to 4 doses of pembrolizumab may be given. The timing of this dose of pembrolizumab can be adjusted based on timing of surgery. Treatment cycles are named according to pembrolizumab treatment. If cycle(s) of pembrolizumab are administered prior to initiation of RT, see section 9.1.10.1.1 for guidance. Weekly visits are only required during RT and the timing of these visits will change if pembrolizumab is administered prior to initiation of RT. All participants may receive no more than 17 cycles. If a dose of pembrolizumab is skipped, see Section 9.1.10.1.1 for guidance on additional treatment cycles.
Radiotherapy (IMRT/IGRT)	X	X	X	X	X	X	(X*)						2 Gy/day in 30 fractions for a total of 60 Gy. *Participants considered high-risk: 2 Gy/day in 33 fractions for a total of 66 Gy. Participants with residual gross tumor; 2 Gy/day in 35 fractions for total of 70 Gy.

Post-surgery Treatment 2 Phase (Arm A/Pembrolizumab)													
Study Period	**Treatment 2 (adjuvant)**												**Notes** Participants that discontinue study treatment for reasons other than an event/disease progression will enter post-treatment study follow-up. Participants who discontinue study treatment due to an event/disease progression will enter Safety and Survival Follow-up. Upon completion of Treatment 2, participants move into post-treatment follow-up.
Visit Number/Title													
Treatment Cycle	**1**			**2**			**3**	**4**	**5**	**6**	**7**	**8-15**	
Week	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**10**	**13**	**16**	**19**	**22-43**	
Scheduled Day(s)	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**	**1**	**1**	**1**	
Scheduling Window (Days, unless noted)	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Conditional Cisplatin Treatment (100 mg/m^2)	X			X			X						Cisplatin will only be administered to participants considered to be high-risk by local pathologist (see Section 9.1.10.2.5 Pathology Specimens for definition), and to participants who do not undergo surgical resection, or have incomplete resection (ie, gross disease left behind). Cisplatin may be administered up to 1 week following completion of RT. To be administered after all procedures/ assessments have been completed. Permitted dose modifications are detailed in Section 7.2.3
Efficacy Procedures													
CT/MRI head and neck, chest, upper abdomen										X		X	For all imaging, the clock will start at the end of RT ± cisplatin. Imaging to be performed 12 weeks (± 7 days) after end of RT ± cisplatin treatment and then every 3 months (91 ± 7 days) until the end of Year 3; then every 6 months (182 ± 14 days) thereafter up to the end of Year 5. Imaging timing should follow calendar days and should not be recalculated based on the date of previous scans.
FDG-PET or FDG-PET/CT										X*			* On-study imaging will be performed as clinically indicated.

Post-surgery Treatment 2 Phase (Arm A/Pembrolizumab)													
Study Period	**Treatment 2 (adjuvant)**												**Notes** Participants that discontinue study treatment for reasons other than an event/disease progression will enter post-treatment study follow-up. Participants who discontinue study treatment due to an event/disease progression will enter Safety and Survival Follow-up. Upon completion of Treatment 2, participants move into post-treatment follow-up.
Visit Number/Title													
Treatment Cycle	**1**			**2**			**3**	**4**	**5**	**6**	**7**	**8-15**	
Week	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**10**	**13**	**16**	**19**	**22-43**	
Scheduled Day(s)	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**	**1**	**1**	**1**	
Scheduling Window (Days, unless noted)	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Patient Reported Outcomes													
EQ-5D-5L	X*			X*						X**		X**	If the participant does not complete the PROs for any reason, the Miss Mode form must be completed to capture the reason the assessment was not performed. * To be completed in conjunction with RT ± cisplatin treatment prior to treatment administration. If adjuvant pembrolizumab is started during the post-surgical recovery phase prior to start of radiotherapy, ePRO assessment should be delayed until radiotherapy begins. ePRO assessments should then be performed on the day RT begins and then repeated during RT treatment on Day 29 ± 3 days. ** To be administered 12 weeks after end of RT ± cisplatin treatment and then every 3 months (91 ± 7 days) until the end of Year 3; then every 12 months (365 days ± 14 days) thereafter up to Year 5. PROs are to be administered by trained site personnel. It is strongly recommended that PROs are completed by participants prior to all procedures/assessments, and in the following order: EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-H&N35.
EORTC QLQ-C30	X*			X*						X**		X**	
EORTC QLQ-H&N35	X*			X*						X**		X**	
Safety Procedures													
Full physical examination including neurological exam	X												
Directed physical examination		X	X	X	X	X	X	X	X	X	X	X	For participants receiving cisplatin: to include routine neurological exam before each dose of cisplatin, thereafter if clinically indicated.

Post-surgery Treatment 2 Phase (Arm A/Pembrolizumab)													
Study Period	**Treatment 2 (adjuvant)**												**Notes** Participants that discontinue study treatment for reasons other than an event/disease progression will enter post-treatment study follow-up. Participants who discontinue study treatment due to an event/disease progression will enter Safety and Survival Follow-up. Upon completion of Treatment 2, participants move into post-treatment follow-up.
Visit Number/Title													
Treatment Cycle	**1**			**2**			**3**	**4**	**5**	**6**	**7**	**8-15**	
Week	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**10**	**13**	**16**	**19**	**22-43**	
Scheduled Day(s)	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**	**1**	**1**	**1**	
Scheduling Window (Days, unless noted)	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	To be assessed prior to dosing.
Weight and Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	Vital signs to be collected include: temperature, resting pulse, resting respiratory rate, blood pressure.
Urine or Serum β-hCG Pregnancy Test (WOCBP only) – as per local SOP	X			(x)			(x)	(x)	(x)	(x)	(x)	(x)	The protocol requires pregnancy testing within 24 hours of the first dose of adjuvant treatment. (x) = a pregnancy test must be performed every month during study treatment. More frequent pregnancy testing may be performed if required by local regulations or if determined necessary by the investigator (refer to Appendix 8 for UK-, Germany- and France-specific requirements).
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	For participants who receive RT alone, labs are to be taken every 3 weeks before each cycle of pembrolizumab. Labs are to be taken up to 3 days prior to pembrolizumab administration. For participants who receive cisplatin, labs are to be taken weekly during RT + cisplatin treatment and thereafter before each cycle. Labs can be taken up to 3 days prior to cisplatin administration and CrCl level assessment is to be repeated within 3 days prior to start of each cisplatin administration for management of dose reduction renal toxicity guidelines. If these labs are within normal range, these labs do not need to be repeated within 24 hours of cisplatin administration. Any abnormal labs should be repeated and assessed within 24 hours of cisplatin administration.
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	

Post-surgery Treatment 2 Phase (Arm A/Pembrolizumab)													
Study Period	**Treatment 2 (adjuvant)**												**Notes** Participants that discontinue study treatment for reasons other than an event/disease progression will enter post-treatment study follow-up. Participants who discontinue study treatment due to an event/disease progression will enter Safety and Survival Follow-up. Upon completion of Treatment 2, participants move into post-treatment follow-up.
Visit Number/Title													
Treatment Cycle	**1**			**2**			**3**	**4**	**5**	**6**	**7**	**8-15**	
Week	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**10**	**13**	**16**	**19**	**22-43**	
Scheduled Day(s)	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**	**1**	**1**	**1**	
Scheduling Window (Days, unless noted)	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Urinalysis	X							X			X	X	Samples to be taken within 3 days prior to pembrolizumab administration. Collected every 2 months at Cycles 1, 4, 7, 10 and 13, unless clinically indicated.
Coagulation tests (PT/INR and aPTT/PTT)	----------As Clinically Indicated----------												Any participant receiving anticoagulant therapy should have coagulation tests monitored closely throughout the study. PTT may be performed if the local lab is unable to perform aPTT
Thyroid Function (TSH)				X					X			X	In case of elevated TSH, to add Free T3 and Free T4. Free T4 should be performed on all participants with an elevated TSH; Free T3 only needs to be performed if it is done as a part of local standard of care. If the Free T3 and Free T4 are not available locally, they can be sent to the central laboratory to be performed (see Laboratory Manual for details). TSH to be tested on Day 1 of every 3rd cycle (ie, Cycles 2, 5, 8, etc), unless clinically indicated.
AE/SAE review	----------Continuous Reporting----------												
Oral and dental check-up	----------Recommended Every 6 months----------												Frequency as per SoC/local guidelines.
Audiometric Testing	----------As Clinically Indicated----------												Follow cisplatin label for ototoxicity management.
Fiber optic examination of primary tumor site									X			X	If clinically indicated. To be performed at Cycles 5, 9 and 13.

Post-surgery Treatment 2 Phase (Arm A/Pembrolizumab)													
Study Period	**Treatment 2 (adjuvant)**												**Notes** Participants that discontinue study treatment for reasons other than an event/disease progression will enter post-treatment study follow-up. Participants who discontinue study treatment due to an event/disease progression will enter Safety and Survival Follow-up. Upon completion of Treatment 2, participants move into post-treatment follow-up.
Visit Number/Title													
Treatment Cycle	**1**			**2**			**3**	**4**	**5**	**6**	**7**	**8-15**	
Week	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**10**	**13**	**16**	**19**	**22-43**	
Scheduled Day(s)	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**	**1**	**1**	**1**	
Scheduling Window (Days, unless noted)	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Future Biomedical Research/Biomarkers													
Blood for RNA Analysis	X					X							For all participants, to be completed in conjunction with RT ± cisplatin treatment prior to treatment administration. For high-risk participants who have approximately 6.5 weeks of RT, blood collection should also align approximately with last dose of RT. If adjuvant pembrolizumab is started during the post-surgical recovery phase prior to start of radiotherapy, the initial blood biomarker collection during adjuvant treatment should be delayed until radiotherapy begins. Blood biomarkers should then be collected on the day RT begins. Whole blood samples should be collected pre-dose. Leftover specimens will be stored for FBR if the participant consents to future biomedical research. For ctDNA collections after end RT, the clock will start at the end of RT ± cisplatin. ctDNA to be collected 12 weeks (± 7 days) after end of RT ± cisplatin treatment and then every 3 months (91 ± 7 days) until end of Year 3; then every 6 months (182 ± 14 days) thereafter up to the end of Year 5. * ctDNA sample should be collected at the end of RT.
Blood for Plasma Biomarker Analyses	X					X							
Blood for Serum Biomarker Analyses	X					X							
Blood for ctDNA	X					X*				X		X	

Post-surgery Treatment 2 Phase (Arm A/Pembrolizumab)													
Study Period	**Treatment 2 (adjuvant)**												**Notes** Participants that discontinue study treatment for reasons other than an event/disease progression will enter post-treatment study follow-up. Participants who discontinue study treatment due to an event/disease progression will enter Safety and Survival Follow-up. Upon completion of Treatment 2, participants move into post-treatment follow-up.
Visit Number/Title													
Treatment Cycle	**1**			**2**			**3**	**4**	**5**	**6**	**7**	**8-15**	
Week	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**10**	**13**	**16**	**19**	**22-43**	
Scheduled Day(s)	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**1**	**1**	**1**	**1**	**1**	
Scheduling Window (Days, unless noted)	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Tumor Tissue Sample Collection													
Tissue Collection for Biomarker Analysis (tested centrally)													Optional biopsy may be collected at recurrence if participant consents.
Neck Dissection (per site discretions) ± biopsy/photography								-----If Clinically Indicated---					Allowed after completion of RT per local SoC.

Refer to Appendix 8 for country-specific requirements.

2.3 Study Screening, Surgery and Post-surgery Treatment 2 Phases (Arm B/SoC)

Study Screening, Surgery and Post-surgery Treatment 2 Phases (Arm B/SoC)														
Study Period	**Screening**	**Treatment randomization**	**Presurgery**	**Surgery**	**Post-surgery Safety Follow-up**	**Treatment 2**							**Notes** Participants that discontinue study treatment for reasons other than an event/disease progression will enter post-treatment study follow-up. Participants who discontinue study treatment due to an event/disease progression will enter Safety and Survival Follow-up. At the end of RT ± cisplatin (Treatment 2), participants in Arm B will enter post-treatment study follow-up. Upon completion of RT ± cisplatin in Treatment 2, participants will enter post-treatment follow-up
Visit Number/Title						**SoC RT ± cisplatin adjuvant**							
Week			**0-4**			**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Scheduled Day (s)	**-28 to -1**		**1**			**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Scheduling Window (Days, unless noted)					**7-30 days post-surgery**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Administrative Procedures													
Informed Consent	X												Documented informed consent must be obtained prior to performing any protocol-specified procedures. Results of a test performed prior to the participant providing documented informed consent as part of routine clinical management are acceptable in lieu of a screening test, if performed within the specified time frame. If the investigator plans to treat beyond the initial radiologic disease progression per RECIST 1.1, additional consent will be required prior to post-progression treatment (see Section 9.1.1.1).
Informed Consent for Future Biomedical Research (FBR; optional)	X												
Participant Identification Card	X	X											Distribute at screening and add the randomization number at the time of randomization.
Inclusion/Exclusion Criteria	X												
Demographics, Disease Details and Complete Medical History (includes substance usage)	X												Substances: alcohol and tobacco.

Study Screening, Surgery and Post-surgery Treatment 2 Phases (Arm B/SoC)														
Study Period	**Screening**	**Treatment randomization**	**Presurgery**	**Surgery**	**Post-surgery Safety Follow-up**	**Treatment 2**							**Notes** Participants that discontinue study treatment for reasons other than an event/disease progression will enter post-treatment study follow-up. Participants who discontinue study treatment due to an event/disease progression will enter Safety and Survival Follow-up. At the end of RT ± cisplatin (Treatment 2), participants in Arm B will enter post-treatment study follow-up. Upon completion of RT ± cisplatin in Treatment 2, participants will enter post-treatment follow-up
Visit Number/Title						**SoC RT ± cisplatin adjuvant**							
Week			**0-4**			**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Scheduled Day (s)	**-28 to -1**		**1**			**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Scheduling Window (Days, unless noted)					**7-30 days post-surgery**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Prior/Concomitant Medication Review	X		X		X	X	X	X	X	X	X	X	Prior medications – Record all medications taken within 28 days of randomization. Concomitant medications – Enter new medications started during the study through the postadjuvant Safety Follow-up visit.
Treatment Randomization via IVRS		X											Participants move straight to SoC surgery following randomization.
Radiotherapy (IMRT/IGRT)						X	X	X	X	X	X	(X*)	2 Gy/day in 30 fractions for a total of 60 Gy *Participants considered high-risk: 2 Gy/day in 33 fractions for a total of 66 Gy. Participants with residual gross tumor: 2 Gy/day in 35 fractions for total of 70 Gy.
Conditional Cisplatin Treatment (100 mg/m^2)						X			X			X	Cisplatin will only be administered to participants considered to be high-risk by local pathologist (see Section 9.1.10.2.5 Pathology Specimens for definition), and to participants who do not undergo surgical resection, or have incomplete resection (ie, gross disease left behind). Cisplatin may be administered up to 1 week following completion of RT. To be administered after all procedures/assessments have been completed. Permitted dose modifications are detailed in Section 7.2.3.

Study Screening, Surgery and Post-surgery Treatment 2 Phases (Arm B/SoC)														
Study Period	**Screening**	**Treatment randomization**	**Presurgery**	**Surgery**	**Post-surgery Safety Follow-up**	**Treatment 2**							**Notes** Participants that discontinue study treatment for reasons other than an event/disease progression will enter post-treatment study follow-up. Participants who discontinue study treatment due to an event/disease progression will enter Safety and Survival Follow-up. At the end of RT ± cisplatin (Treatment 2), participants in Arm B will enter post-treatment study follow-up. Upon completion of RT ± cisplatin in Treatment 2, participants will enter post-treatment follow-up
Visit Number/Title						**SoC RT ± cisplatin adjuvant**							
Week			**0-4**			**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Scheduled Day (s)			**1**			**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Scheduling Window (Days, unless noted)	**-28 to -1**				**7-30 days post-surgery**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Surgery				X									Performed as part of planned SoC. Participants who do not undergo surgery as originally planned, for reasons other than centrally verified radiographic disease progression, may proceed to Treatment 2 and receive salvage RT plus cisplatin.
Efficacy Procedures													
CT/MRI head and neck, chest, upper abdomen	X		X*		(X) optional at site discretion								If the participant had received CT/MRI scan prior to providing documented informed consent and within 28 days prior to randomization, the assessment can be accepted. For each participant, the same modality should be used throughout the study for response evaluation. The upper abdominal CT/MRI should cover the liver in its entirety. *The screening scans will serve as presurgery scans except if the baseline scans are done >14 days prior to the date of surgery, then repeat imaging prior to surgery is required.
FDG-PET or FDG-PET/CT	X												If the participant had received FDG-PET or FDG-PET/CT scan prior to providing documented informed consent and within 28 days prior to randomization, the assessment can be accepted.
Tissue Collection for Histopathology (mPR and pCR assessment)				X									Assessment of surgical margins / gross lesions will be performed by the local pathologist.

Study Screening, Surgery and Post-surgery Treatment 2 Phases (Arm B/SoC)														
Study Period	**Screening**	**Treatment randomization**	**Presurgery**	**Surgery**	**Post-surgery Safety Follow-up**	**Treatment 2**							**Notes** Participants that discontinue study treatment for reasons other than an event/disease progression will enter post-treatment study follow-up. Participants who discontinue study treatment due to an event/disease progression will enter Safety and Survival Follow-up. At the end of RT ± cisplatin (Treatment 2), participants in Arm B will enter post-treatment study follow-up. Upon completion of RT ± cisplatin in Treatment 2, participants will enter post-treatment follow-up
Visit Number/Title						**SoC RT ± cisplatin adjuvant**							
Week			**0-4**			**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Scheduled Day (s)			**1**			**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Scheduling Window (Days, unless noted)	**-28 to -1**				**7-30 days post-surgery**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Patient Reported Outcomes													
EQ-5D-5L			X			X*			X*				If the participant does not complete the PROs for any reason, the Miss Mode form must be completed to capture the reason the assessment was not performed. * To be completed in conjunction with RT ± cisplatin treatment prior to treatment administration ePRO assessments should be performed on day RT begins and then repeated during RT treatment on Day 29 ± 3 days. PROs are to be administered by trained site personnel. It is strongly recommended that PROs are completed by participants prior to all procedures/assessments, and in the following order: EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-H&N35.
EORTC QLQ-C30			X			X*			X*				
EORTC QLQ-H&N35			X			X*			X*				
Safety Procedures													
Full physical examination including neurological exam and Height*	X				X								To be performed by the investigator or qualified designee. Documented routine neurological exams performed within 6 weeks of randomization are acceptable and do not need to be repeated in Screening. *Height will be measured at Screening only.

Study Screening, Surgery and Post-surgery Treatment 2 Phases (Arm B/SoC)														
Study Period	**Screening**	**Treatment randomization**	**Presurgery**	**Surgery**	**Post-surgery Safety Follow-up**	**Treatment 2**							**Notes** Participants that discontinue study treatment for reasons other than an event/disease progression will enter post-treatment study follow-up. Participants who discontinue study treatment due to an event/disease progression will enter Safety and Survival Follow-up. At the end of RT ± cisplatin (Treatment 2), participants in Arm B will enter post-treatment study follow-up. Upon completion of RT ± cisplatin in Treatment 2, participants will enter post-treatment follow-up
Visit Number/Title						**SoC RT ± cisplatin adjuvant**								
Week			**0-4**			**1**	**2**	**3**	**4**	**5**	**6**	**7**		
Scheduled Day (s)	**-28 to -1**		**1**			**1**	**8**	**15**	**1**	**8**	**15**	**1**		
Scheduling Window (Days, unless noted)					**7-30 days post-surgery**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Directed physical examination			X			X	X	X	X	X	X	X	To be performed by the investigator or qualified designee. For participants receiving cisplatin: directed physical examination to include neurological exam before each dose of cisplatin.	
ECOG Performance Status	X		X		X	X	X	X	X	X	X	X	Screening (within 10 days prior to the start of study randomization). Investigator or designee to confirm no deterioration prior to surgery. ECOG performance status must be 0 or 1 presurgery. To be assessed prior to dosing.	
Weight and Vital Signs	X		X		X	X	X	X	X	X	X	X	Vital signs to be collected include: temperature, resting pulse, resting respiratory rate, blood pressure.	
12-lead ECG (local)	X													
Urine or Serum β-hCG Pregnancy Test (WOCBP only) – as per local SOP	X				(x)	X			(x)			(x)	The protocol requires pregnancy testing at Screening, within 24 hours (urine) or within 72 hours (serum) before randomization, and within 24 hours of the first dose of adjuvant treatment. (x) = a pregnancy test must be performed every month during study treatment. More frequent pregnancy testing may be performed if required by local regulations or if determined necessary by the investigator (refer to Appendix 8 for UK-, Germany-, and France-specific requirements).	

Study Screening, Surgery and Post-surgery Treatment 2 Phases (Arm B/SoC)														
Study Period	**Screening**	**Treatment randomization**	**Presurgery**	**Surgery**	**Post-surgery Safety Follow-up**	**Treatment 2**							**Notes** Participants that discontinue study treatment for reasons other than an event/disease progression will enter post-treatment study follow-up. Participants who discontinue study treatment due to an event/disease progression will enter Safety and Survival Follow-up. At the end of RT ± cisplatin (Treatment 2), participants in Arm B will enter post-treatment study follow-up. Upon completion of RT ± cisplatin in Treatment 2, participants will enter post-treatment follow-up
Visit Number/Title						**SoC RT ± cisplatin adjuvant**							
Week			**0-4**			**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Scheduled Day (s)	**-28 to -1**		**1**			**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Scheduling Window (Days, unless noted)					**7-30 days post-surgery**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
HIV, hepatitis B and C screen (testing optional per site SOP)	X												HIV, hepatitis B and C testing are required when mandated by local health authority. Refer to Appendix 8 for Germany-specific requirements for HIV, Hepatitis B and C testing.
Hematology	X		X*		X	X	X	X	X	X	X	X	After Day 1, lab samples can be collected up to 3 days prior to the scheduled time point. During adjuvant treatment, labs are to be taken as per SoC for participants who receive RT alone and weekly if cisplatin is administered. Labs can be taken up to 3 days prior to cisplatin administration and CrCl level assessment is to be repeated within 3 days prior to start of each cisplatin administration for management of dose reduction renal toxicity guidelines. If these labs are within normal range, these labs do not need to be repeated within 24 hours of cisplatin administration. Any abnormal labs should be repeated and assessed within 24 hours of cisplatin administration. *Labs at presurgery visit do not need to be repeated if presurgery visit occurs within 3 days of randomization.
Chemistry	X		X*		X	X	X	X	X	X	X	X	
Urinalysis	X		--If Clinically Indicated--		X	X	--If Clinically Indicated--						After Day 1 samples can be collected up to 3 days prior to the scheduled time point.

Study Screening, Surgery and Post-surgery Treatment 2 Phases (Arm B/SoC)

Study Period	**Screening**	**Treatment randomization**	**Presurgery**	**Surgery**	**Post-surgery Safety Follow-up**	**Treatment 2**							**Notes**
Visit Number/Title						**SoC RT ± cisplatin adjuvant**							Participants that discontinue study treatment for reasons other than an event/disease progression will enter post-treatment study follow-up. Participants who discontinue study treatment due to an event/disease progression will enter Safety and Survival Follow-up. At the end of RT ± cisplatin (Treatment 2), participants in Arm B will enter post-treatment study follow-up. Upon completion of RT ± cisplatin in Treatment 2, participants will enter post-treatment follow-up
Week			**0-4**			**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Scheduled Day (s)			**1**			**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Scheduling Window (Days, unless noted)	**-28 to -1**				**7-30 days post-surgery**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Coagulation tests (PT/INR and aPTT/PTT)	X				----If Clinically Indicated-----								Any participant receiving anticoagulant therapy should have coagulation tests monitored closely throughout the study. PTT may be performed if the local lab is unable to perform aPTT.
Thyroid Function (TSH)	X		X*						X				In case of elevated TSH, to add Free T3 and Free T4. Free T4 should be performed on all participants with elevated TSH; Free T3 only needs to be performed if it is done as a part of local standard of care. If the Free T3 and Free T4 are not available locally, they can be sent to the central laboratory to be performed (see Laboratory Manual for details). *Laboratory tests at presurgery visit do not need to be repeated if presurgery visit occurs within 3 days of randomization.
AE/SAE review	X		-------Continuous Reporting-------										
Oral and dental check-up	X					---Recommended Every 6 months---							Frequency as per SoC/local guidelines.
Audiometric Testing	X					----If Clinically Indicated----							Follow cisplatin label for ototoxicity management. Documented routine exams performed within 6 weeks of randomization are acceptable and do not need to be repeated in Screening.
Fiber optic examination of primary tumor site	X					----If Clinically Indicated----							Documented routine exams performed within 6 weeks of randomization are acceptable and do not need to be repeated in Screening.

Study Screening, Surgery and Post-surgery Treatment 2 Phases (Arm B/SoC)														
Study Period	**Screening**	**Treatment randomization**	**Presurgery**	**Surgery**	**Post-surgery Safety Follow-up**	**Treatment 2**							**Notes** Participants that discontinue study treatment for reasons other than an event/disease progression will enter post-treatment study follow-up. Participants who discontinue study treatment due to an event/disease progression will enter Safety and Survival Follow-up. At the end of RT ± cisplatin (Treatment 2), participants in Arm B will enter post-treatment study follow-up. Upon completion of RT ± cisplatin in Treatment 2, participants will enter post-treatment follow-up
Visit Number/Title						**SoC RT ± cisplatin adjuvant**							
Week			**0-4**			**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Scheduled Day (s)			**1**			**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Scheduling Window (Days, unless noted)	**-28 to -1**				**7-30 days post-surgery**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Future Biomedical Research/Biomarkers													
Blood for Genetic Analysis [a]			X										
Blood for RNA Analysis			X			X							For all participants, to be completed in conjunction with RT ± cisplatin treatment prior to treatment administration. Whole blood samples should be collected pre-dose. Leftover specimens will be stored for FBR if the participant consents to FBR. * ctDNA sample should be collected at the end of RT.
Blood for Plasma Biomarker Analyses			X			X							
Blood for Serum Biomarker Analyses			X			X							
Blood for ctDNA			X			X					X*	X*	
Tumor Tissue Sample Collection													
Histology, including PD-L1 and p16 biomarker analysis on all participants prior to randomization for stratification, p16 evaluations [b]	X												Tumor tissue from core or excisional biopsy (FNA not adequate) from all participants. Results of PD-L1 testing are required for stratification; p16 testing required only for participants with oropharyngeal cancer. PD-L1 tested centrally and p16 biomarker analysis tested locally/centrally.
Tissue Collection for Biomarker Analysis [b]	X			X*									Core or excisional biopsy (FNA not adequate). *For participants who do not achieve a pCR, a tumor tissue sample is to be collected and submitted to the designated central laboratory for translational research.

Study Screening, Surgery and Post-surgery Treatment 2 Phases (Arm B/SoC)														
Study Period	**Screening**	**Treatment randomization**	**Presurgery**	**Surgery**	**Post-surgery Safety Follow-up**	**Treatment 2**							**Notes** Participants that discontinue study treatment for reasons other than an event/disease progression will enter post-treatment study follow-up. Participants who discontinue study treatment due to an event/disease progression will enter Safety and Survival Follow-up. At the end of RT ± cisplatin (Treatment 2), participants in Arm B will enter post-treatment study follow-up. Upon completion of RT ± cisplatin in Treatment 2, participants will enter post-treatment follow-up
Visit Number/Title						**SoC RT ± cisplatin adjuvant**							
Week			**0-4**			**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Scheduled Day (s)			**1**			**1**	**8**	**15**	**1**	**8**	**15**	**1**	
Scheduling Window (Days, unless noted)	**-28 to -1**				**7-30 days post-surgery**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	
Neck Dissection (per site discretions) ± biopsy/photography						----------If Clinically Indicated------							Allowed after completion of RT per local SoC.

Refer to Appendix 8 for country-specific requirements.

[a] This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for Future Biomedical Research (FBR) if the participant (or their legally acceptable representative) provides documented informed consent for FBR. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

[b] Baseline tumor tissue from a core or excisional biopsy (FNA not adequate) from participants with oropharyngeal cancer must be tested locally for HPV status (if HPV status not known) prior to randomization. If local p16 testing results are not available, or cannot be assessed locally by the specified method, a tumor tissue sample must be submitted for p16 testing at the designated central laboratory. For all participants, baseline tumor tissue must also be provided to the central vendor for PD-L1 biomarker testing (results required prior to randomization) and translational research. Refer to Section 9.2.2 for additional information about tissue requirements. Detailed instructions for tissue collection, process and shipment are provided in the Vendor Manual. If the participant provides documented informed consent for FBR, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR. Newly obtained biopsies are permitted.

2.4 End of Treatment and Follow-up Visits (Arms A and B)

End of Treatment and Follow-up Visits (Arms A and B)							
Study Period	**End of Treatment**	**Post-Treatment Follow-up[a]**					**Notes**
Visit Number/Title	**Discontinuation**	**Safety FU**	**Post-Treatment FU**			**Survival FU**	
Treatment Cycle/Day			**Up to end of Year 3**	**Years 4-5**			
Scheduling Window (Days (unless noted)	**At time of Treatment Discontinuation**	**30 days from last dose +14 days**	**Every 3 months from last scan ±7 days**	**Q6M ±14 days**	**Q12M ±14 days**	**Every 3 months ±14 days**	
Administrative Procedures							
Prior/Concomitant Medication Review	X	X	----If Clinically Indicated---				
Post-study Anticancer Therapy Status						X	By telephone contact in Survival FU. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study. Participants who do not/will not have a scheduled study visit during the Sponsor-defined time period will be contacted by telephone for their survival status (excluding participants that have had a death event previously recorded). After 5 years, participants will be followed by telephone to monitor survival and anticancer treatment status every 6 months (±1 month) for overall survival and/or other anticancer treatment until consent withdrawal from study, becoming lost to follow-up, death or end of the study, whichever is earlier.
Survival status	<---------->					X	

End of Treatment and Follow-up Visits (Arms A and B)							
Study Period	**End of Treatment**	**Post-Treatment Follow-up[a]**					**Notes**
Visit Number/Title	**Discontinuation**	**Safety FU**	**Post-Treatment FU**			**Survival FU**	
Treatment Cycle/Day			**Up to end of Year 3**	**Years 4-5**			
Scheduling Window (Days (unless noted)	**At time of Treatment Discontinuation**	**30 days from last dose +14 days**	**Every 3 months from last scan ±7 days**	**Q6M ±14 days**	**Q12M ±14 days**	**Every 3 months ±14 days**	
Efficacy Procedures							
CT/MRI head and neck, chest, upper abdomen			X	X		*[X]	For all imaging, the clock will start at the end of RT ± cisplatin. Imaging to be performed 12 weeks (± 7 days) after end of RT ± cisplatin treatment and then every 3 months (91 ± 7 days) until the end of Year 3; then every 6 months (182 ± 14 days) thereafter up to the end of Year 5. Imaging timing should follow calendar days and should not be recalculated based on the date of previous scans. The upper abdominal CT/MRI should cover the liver in its entirety. Continuation of imaging/biopsies is strongly recommended for participants who have not yet experienced an event/progression and have started a new anticancer treatment. *Additionally, imaging assessment/biopsies performed as part of SOC to evaluate disease status for participants in survival follow-up who have not yet experienced an event/progression should be collected during survival follow-up. All available images should be submitted to the central imaging vendor and recorded in the applicable eCRF.

End of Treatment and Follow-up Visits (Arms A and B)							
Study Period	**End of Treatment**	**Post-Treatment Follow-up[a]**					**Notes**
Visit Number/Title	**Discontinuation**	**Safety FU**	**Post-Treatment FU**			**Survival FU**	
Treatment Cycle/Day			**Up to end of Year 3**	**Years 4-5**			
Scheduling Window (Days (unless noted)	**At time of Treatment Discontinuation**	**30 days from last dose +14 days**	**Every 3 months from last scan ±7 days**	**Q6M ±14 days**	**Q12M ±14 days**	**Every 3 months ±14 days**	
EQ-5D-5L	X	X	X		X		To be administered 12 weeks after end of RT ± cisplatin treatment and then every 3 months (91 ± 7 days) until end of Year 3; then every 12 months (365 ± 14 days) thereafter up to the end of Year 5. PROs are to be administered by trained site personnel. It is strongly recommended that PROs are completed by participants prior to all procedures/assessments, and in the following order: EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-H&N35. If the participant does not complete the PROs for any reason, the Miss Mode form must be completed to capture the reason the assessment was not performed.
EORTC QLQ-C30	X	X	X		X		
EORTC QLQ-H&N35	X	X	X		X		
Safety Procedures							
Full physical examination	X						To be performed by the investigator or qualified designee. To include neurological exam if clinically indicated
Directed physical examination		X	X	X			
ECOG Performance Status	X	X	X	X			
Weight and Vital Signs	X	----If Clinically Indicated------					To include: temperature, heart rate, respiratory rate, blood pressure.

End of Treatment and Follow-up Visits (Arms A and B)							
Study Period	**End of Treatment**	**Post-Treatment Follow-up[a]**					**Notes**
Visit Number/Title	**Discontinuation**	**Safety FU**	**Post-Treatment FU**			**Survival FU**	
Treatment Cycle/Day			**Up to end of Year 3**	**Years 4-5**			
Scheduling Window (Days (unless noted)	**At time of Treatment Discontinuation**	**30 days from last dose +14 days**	**Every 3 months from last scan ±7 days**	**Q6M ±14 days**	**Q12M ±14 days**	**Every 3 months ±14 days**	
Urine or Serum β-hCG Pregnancy Test (WOCBP only) – as per local SOP	X*	X					*A pregnancy test is required at end of treatment for participants completing study treatment and participants who discontinue study treatment early. Monthly pregnancy testing should continue in post-treatment until 120 days after last dose of pembrolizumab and 180 days after last dose of cisplatin and/or radiotherapy. More frequent pregnancy testing may be performed if required by local regulations or if determined necessary by the investigator (refer to Appendix 8 for UK-, Germany- and France-specific requirements).
Hematology, Chemistry, Urinalysis	X	X	--If Clinically Indicated--				Unresolved abnormal lab results associated with drug-related AEs should be followed until resolution.
Coagulation tests (PT/INR and aPTT/PTT)		------If Clinically Indicated------					
Thyroid Function (TSH)	X	X	---If Clinically Indicated---				TSH; in case of elevated TSH to add Free T3 and Free T4. Free T4 should be performed on all participants with elevated TSH; Free T3 only needs to be performed if it is done as a part of local standard of care. If the Free T3 and Free T4 are not available locally, they can be sent to the central laboratory to be performed (see Laboratory Manual for details).

End of Treatment and Follow-up Visits (Arms A and B)							
Study Period	**End of Treatment**	**Post-Treatment Follow-up[a]**					**Notes**
Visit Number/Title	**Discontinuation**	**Safety FU**	**Post-Treatment FU**			**Survival FU**	
Treatment Cycle/Day			**Up to end of Year 3**	**Years 4-5**			
Scheduling Window (Days (unless noted)	**At time of Treatment Discontinuation**	**30 days from last dose +14 days**	**Every 3 months from last scan ±7 days**	**Q6M ±14 days**	**Q12M ±14 days**	**Every 3 months ±14 days**	
AE/SAE review	----------Continuous Reporting----------						All AEs occurring up until 30 days following end of study treatment and SAEs occurring up until 90 days following end of treatment or 30 days if the participant initiates new anticancer therapy, whichever is earlier should be reported. Treatment-related late toxicity may be collected for up to 5 years.
Oral and dental check-up			---- Recommended every 6 months---				Frequency as per SoC/local guidelines.
Audiometric Testing	------If Clinically Indicated------						
Fiber optic examination of primary tumor site			------Every 12 months---- or as per site discretion				
Future Biomedical Research/Biomarkers							
Blood for RNA Analysis	X						
Blood for Plasma Biomarker Analyses	X						
Blood for Serum Biomarker Analyses	X						
Blood for ctDNA	X		X*	X*			*For ctDNA collections after end RT, the clock will start at the end of RT ± cisplatin. ctDNA to be collected 12 weeks (± 7 days) after end of RT ± cisplatin treatment and then every 3 months (91 ± 7 days) until end of Year 3; then every 6 months (182 ± 14 days) thereafter up to the end of Year 5.
Tumor Tissue Sample Collection							
Tissue Collection for Biomarker Analysis (tested centrally)							Optional biopsy may be collected at recurrence if participant consents.

Refer to Appendix 8 for country-specific requirements.

[a] In participants who discontinue study therapy without an event/disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 3 months (91 ± 7 days) until end of Year 3 (measured from the date of randomization); thereafter every 6 months (182 ± 14 days) until end of Year 5, until (1) an event/disease progression, (2) pregnancy, (3) withdrawal of consent, (4) death, or (5) the end of the study, whichever occurs first.
A participant may discontinue from study treatment for reasons other than disease recurrence/progression or start of a new anticancer therapy but will remain in the study for post-treatment follow-up for disease progression as outlined in Section 8, as long as the participant does not withdraw consent for post-treatment follow-up for disease progression.
Participants who discontinue study treatment due to an event/disease progression will enter Survival Follow-up.

3 INTRODUCTION

Pembrolizumab as neoadjuvant therapy and in combinations with standard of care (SoC) radiotherapy (RT) with/without cisplatin as adjuvant therapy is being investigated for participants with newly diagnosed Stage III/IVA, resectable, locoregionally advanced head and neck squamous cell cancers (LA HNSCC). Its efficacy and safety are being evaluated against SoC treatment in this randomized, open-label, Phase III study.

Pembrolizumab (trade name Keytruda®) is a potent and highly selective humanized monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4) / kappa isotype designed to directly block the interaction between Programmed Cell Death 1 (PD-1) receptor and its ligands, Programmed Death Ligand 1 (PD-L1) and Programmed Death Ligand 2 (PD-L2). This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection.

Pembrolizumab is currently in clinical development for a number of advanced malignancies. For more detail on specific indications, please refer to the Pembrolizumab Investigator's Brochure.

3.1 Study Rationale

Pembrolizumab has demonstrated durable clinical activity in participants with recurrent/metastatic HNSCC and was granted accelerated approval for participants with recurrent/metastatic HNSCC with disease progression on or after platinum-containing chemotherapy by Food and Drug Administration (FDA) on 05-Aug-2016. In addition, preliminary data from 21 participants in a Phase II Merck Investigator Studies Program (MISP) study, presented at the American Society of Clinical Oncology (ASCO) Annual Meeting 2017, evaluating preoperative pembrolizumab prior to resection in resectable LA HNSCC at high risk for recurrence (eg, T4 or Stage IVB) demonstrated treatment effect in the pathological samples in 43% of participants, and clinical-to-pathologic downstaging at the time of surgery in 48% of participants (NCT02296684). Thirty-eight percent of patients had high risk pathologic features compared to an expected rate of 80%. At the time of presentation, no unexpected surgical delays or complications had been observed.

Considering the potential activity of pembrolizumab with durable responses and tumor downstaging further investigation of neoadjuvant and adjuvant combinations in a larger study to compare efficacy and safety against SoC is warranted. The objective of this study is to evaluate whether pembrolizumab as neoadjuvant therapy can increase pathological response in the surgical specimen and as adjuvant therapy can increase locoregional control in combination with SoC RT ± cisplatin in a high-risk population with newly diagnosed resectable LA HNSCC.

3.2 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 intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T-cell. For more details on specific indications refer to the Investigator's brochure.

3.2.1 Pharmaceutical and Therapeutic Background

Head and neck squamous cell carcinoma is the seventh most common cancer worldwide with around 600,000 new cases diagnosed per year [Siegel, R., et al 2013]. The most frequent tumor sites of HNSCC are the larynx, the pharynx, and the oral cavity.

Alcohol and tobacco consumption are the main risk factors for oral cavity, larynx, oropharynx, and hypopharynx cancers and account for 75% of HNSCC. In addition, the oncogenic human papillomavirus (HPV) infection, mainly HPV-16, is an established cause of oropharyngeal cancer (tonsils and base of tongue) [Ang, K. K., et al 2010] [Gillison, M. L. 2004]. Globally, the incidence of HPV-induced oropharyngeal cancer increases, but varies from less than 10% to 70% of all oropharyngeal cancers depending on the geographic area, being more frequent in industrialized countries. The etiologic role of HPV in other HNSCC sites than oropharynx is unclear.

Treatment choice depends on the location of the primary tumor, stage of the disease, and expected oncological and functional outcomes. Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) early stage (I/II) HNSCC is usually treated with single modality therapy, ie, surgery or RT. The management of locally advanced disease (UICC/AJCC Stage III/IV) generally requires various combinations of RT, surgery, and chemotherapy or cetuximab. The survival rates for all participants with HNSCC are around 70% at 1 year and 40-60% at 5 years.

Factors that affect clinical outcome of patients with LA HNSCC include performance status, tumor stage at diagnosis, and HPV status. Expression of p16 is highly correlated to infection with HPV in oropharyngeal cancer [Lassen, P., et al 2009] [Weinberger, P. M., et al 2006] and the strong prognostic impact of p16-immunohistochemistry for oropharyngeal cancer has been demonstrated in several clinical studies [Ang, K. K., et al 2010] [Lassen, P., et al 2009] [Lassen, P., et al 2011] [Lassen, P., et al 2010]. The prevalence of HPV positivity varies by stage of disease, with frequencies in HPV endemic areas reported at 50%-59% in local disease (or Stages I/II), 75%-78% in regional disease (or Stages III-IVB), and 67% in distant metastatic disease [OSullivan, B., et al 2016] [Steinau, M., et al 2014].

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 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].

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 immunoglobulin (Ig) superfamily member related to CD28 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) which 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 Ig-variable–type domain responsible for ligand binding and a cytoplasmic tail responsible for 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 Src homology region 2 domain-containing phosphatase (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 CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (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 LA HNSCC.

Keytruda® is currently approved in the United States (US) and in several global locations for the treatment of recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

3.2.2 Pre-clinical and Clinical Studies

Details of preclinical and clinical studies are provided in the Investigator's Brochure.

Clinical studies with pembrolizumab have demonstrated efficacy in participants with advanced melanoma, non-small cell lung cancer, head and neck cancer (HNC), bladder cancer, Hodgkin's lymphoma, and microsatellite instability (MSI) high cancers.

3.2.3 Ongoing Clinical Studies

There is an expansive ongoing research program of clinical studies evaluating pembrolizumab in patients with a number of hematological and solid malignancies, including HNC. For study details please refer to the Investigator's Brochure.

The clinical program for HNSCC consists of the completed and ongoing studies for recurrent/metastatic disease (KN012, KN055, KN040, KN048, and KN412), as well as this study, KN689.

Analyses from studies KN012, KN055, KN040 and KN048 demonstrate clinical activity in participants with recurrent/metastatic disease. In addition, the overall number, type, and frequency of adverse events (AEs) and serious adverse events (SAEs) reported in these studies are representative of patients with HNSCC and are not indicative of any new safety concerns for this program.

KEYNOTE-012 (KN012)

KN012 is a Phase IB, multi-cohort study evaluating the single-agent activity of pembrolizumab in various solid tumors, including 2 cohorts of participants (Cohorts B and B2) with recurrent/metastatic HNSCC. Cohort B consisted of 60 participants with PD-L1 positive HNSCC who received pembrolizumab 10 mg/kg every 2 weeks (Q2W). Cohort B2 consisted of 132 participants regardless of PD-L1 status, who received pembrolizumab 200 mg every 3 weeks (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 recurrent/metastatic disease. Enrollment is closed, but participants are ongoing in the study.

The efficacy and safety results after long term follow-up based on pooled data from Cohorts B and B2 were presented at ASCO 2016 [Mehra, R., et al 2016]. In the recurrent/metastatic HNSCC population (n=192), the objective response rate (ORR) was 21.9% (95% confidence interval [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 (tumor proportion scoring, TPS), there was no statistically significant increase ORR with PD-L1 positive (≥1) versus (vs.) negative (<1) tumors. Conversely, when immune cells were included in the scoring system (CPS), PD-L1 expression on tumor and immune cells significantly correlated with ORR, progression free survival (PFS), and overall survival (OS) [Chow, L. Q., et al 2016]. The ORR with pembrolizumab is greater than that of existing standard single-agent cytotoxic chemotherapies such as methotrexate, which in the setting of second-line recurrent/metastatic disease has an ORR of approximately 4%. 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%.

Importantly, the responses seen with pembrolizumab were durable. Among participants with recurrent/metastatic HNSCC, the median duration of response (DOR) ranged from 1.8+ to 21.8+ months, and the median was not reached. Among participants who progressed, 85% were in response for the at least 6 months, and 71% of responders had ongoing responses.

Efficacy and safety of pembrolizumab based on additional long-term follow-up in KN012 was subsequently reported [Mehra, R., et al 2018]. Median follow-up was 9 months (range 0.2-32). No deaths due to treatment were observed. ORR was 18% (34/192; 95% CI, 13%-24%). Eight patients (4%) experienced CR and 26 (14%) patients experienced PR. Eighty

five percent of responses lasted ≥ 6 months and OS at 12 months was 38%. The median time to response was 2 months (range 2 to 17 months). Median DOR was not reached (range 2+ to 30+ months).

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 II, nonrandomized, single cohort study of pembrolizumab (200 mg Q3W) monotherapy in a heavily pretreated population of patients with recurrent/metastatic HNSCC who have progressed on prior platinum and cetuximab therapy. Results from 171 participants treated with pembrolizumab were presented by Bauml et al [Bauml, J., et al 2017]. When confirmed responses were evaluated, the ORR was 16% (complete response, n=1; partial response, 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 confirm findings from KN012 in the recurrent/metastatic HNSCC population; pembrolizumab monotherapy demonstrates consistent and clinically meaningful activity of pembrolizumab 200 mg Q3W in heavily pretreated participants with HNSCC.

KEYNOTE-040 (KN040)

KN040 is an ongoing Phase III, randomized, active-controlled, open-label study of pembrolizumab versus the choice of 3 different SoC therapies in participants with recurrent/metastatic HNSCC. Approximately 495 participants with recurrent/metastatic HNSCC were stratified by Eastern Cooperative Oncology Group (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), before being randomized 1:1 to receive pembrolizumab 200 mg Q3W or the investigator's choice of one of the following therapies, to be chosen prior to randomization: single agent methotrexate, single agent docetaxel, or single agent cetuximab, for up to 2 years. The primary objective of the study is to evaluate OS in participants with recurrent/metastatic HNSCC treated with pembrolizumab compared to SoC treatment. Enrollment is closed, but participants are receiving ongoing treatment in the study.

The efficacy and safety data from the final analysis were reported in The Lancet in 2019 [Cohen, E. E. W., et al 2019]. As of the data cut-off 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 overall survival in the Intention-To-Treat 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). The HR for all examined subgroups was similar. Fewer patients treated with pembrolizumab than with SOC had grade 3 or worse treatment-related adverse events (33 [13%] of 246 vs 85 [36%] of 234).

For participants with a PD-L1 CPS of 1 or higher, the HR for death was 0.74 (95% CI 0.58-0.93; nominal *p*=0.0049). Median survival was 8.7 months (95% CI 6.9-11.4) with pembrolizumab and 7.1 months (5.7-8.3) with standard of care. For participants with a PD-L1 CPS less than 1, the HR for death was 1.28 (95% CI 0.80-2.07; *p*=0.8476). Median overall survival was 6.3 months (3.9-8.9) in the pembrolizumab group and 7 months (5.1-9.0) in the standard-of-care group.

In participants with a PD-L1 TPS of 50% or higher, the HR for death was 0.53 (95% CI 0.35-0.81; nominal *p*=0.0014). Median overall survival was 11.6 months (95% CI 8.3-19.5) with pembrolizumab and 6.6 months (4.8-9.2) with standard of care. In participants with a PD-L1 TPS of less than 50%, the HR was 0.93 (95% CI 0.73-1.17; *p*=0.2675) with pembrolizumab. Median overall survival was 6.5 months (95% CI 5.6-8.8) with pembrolizumab and 7.1 months (95% CI 5.7-8.1) with standard of care.

The median duration of response was 18.4 months in the pembrolizumab group compared with only 5 months in the SOC group. In summary, the responses to pembrolizumab for this patient population was durable, similar to the KN012 and KN055 studies. In addition, the benefit of pembrolizumab compared with SOC was greater in patients with PD-L1 expression on their tumors or in the tumor microenvironment compared to those without PD-L1 expression. The safety profile was also better for pembrolizumab than compared to the SOC.

KEYNOTE-048 (KN048)

KN048 is an ongoing Phase III, 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 advanced HNC. A total of 882 participants with first-line recurrent or metastatic HNSCC were randomized worldwide 1:1:1 between the 3 arms of the study to examine the efficacy and safety of pembrolizumab (n= 301 subjects), pembrolizumab plus chemotherapy (n= 281 subjects) versus SoC with cetuximab and chemotherapy (n= 300 subjects). Prior to randomization, participants were 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 Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 as assessed by blinded independent central review (BICR), and OS. Enrollment is closed, but participants are receiving ongoing treatment in the study.

The data presented at European Society of Medical Oncology (ESMO) 2018 for KEYNOTE-048, compared pembrolizumab monotherapy, and pembrolizumab + chemotherapy (platinum based chemotherapy plus fluorouracil) to the EXTREME regimen (platinum based chemotherapy plus fluorouracil and cetuximab) for first-line treatment of R/M HNSCC [Burtness, B., et al 2018]. Pembrolizumab monotherapy demonstrated a higher OS when compared to the EXTREME regimen in R/M HNSCC that expressed PD-L1. The data in participants with combined positive score (CPS ≥ 20) yielded OS that was significantly longer with pembrolizumab than the EXTREME regimen (HR 0.61, [95% CI 0.45-0.83]; *p*=0.0007; median 14.9 vs. 10.7 months). The results were similar in participants with a lower cut point of PD-L1 expression (CPS ≥ 1). For this population, HR 0.78 (95% CI 0.64-0.96); *p*=0.0086 and the median OS was 12.3 vs. 10.3 months. In addition, OS for pembrolizumab was noninferior to the EXTREME regimen.

Confirmed ORR (pembrolizumab versus EXTREME) was 23% vs 36% for CPS ≥20, 19% vs 35% for CPS ≥ 1, and 17% vs 36% for the total population. Median DOR (pembrolizumab versus EXTREME) was 20.9 vs 4.2 months for CPS ≥20, 20.9 versus 4.5 months for CPS ≥ 1, and 20.9 vs 4.5 months for the total population. For the pembrolizumab arm Grade 3-5 AE rates were 17% compared to 69% for the EXTREME arm. Pembrolizumab + chemotherapy significantly improved OS in this total population (HR 0.77 [95% CI 0.63-0.93]; *p*=0.0034; median 13.0 vs 10.7 months,). The safety profiles for pembrolizumab + chemotherapy and the EXTREME regimen were comparable.

In summary, for first-line R/M HNSCC, pembrolizumab significantly improved OS over the EXTREME regimen in both the CPS ≥ 20 and CPS ≥ 1 populations and was also noninferior in the total population with a favorable toxicity profile. Pembrolizumab plus chemotherapy improved OS in the total population with a comparable safety profile. Responses to pembrolizumab were durable, and safety was comparable to EXTREME regimen. Therefore, pembrolizumab based treatment may be established as a new first-line standard of care for R/M HNSCC.

KEYNOTE-412 (KN412)

KN412 is an ongoing, Phase III, randomized, placebo-controlled, multi-site, triple-blind, two arm study to determine the efficacy and safety of pembrolizumab given concomitantly with chemoradiation (CRT) and as maintenance therapy, versus placebo plus CRT in participants with LA HNSCC. Participants will be stratified at randomization by tumor site/p16 status (Oropharynx – p16 positive vs. Oropharynx – p16 negative vs. tumor site other than oropharynx), Stage III versus Stage IV, and RT regimen (accelerated fractionation vs. standard fractionation). Approximately 780 participants will be randomly assigned 1:1 to receive either: CRT plus pembrolizumab 200 mg Q3W; or CRT plus placebo (Q3W). Chemotherapy will include cisplatin 100 mg/m^2 IV on Days 8, 29, and 50 of RT. A primary objective in this study is to compare event-free survival (EFS) per RECIST 1.1 as assessed by BICR between treatment arms.

3.3 Benefit/Risk Assessment

Participants will receive SoC treatment or SoC treatment plus the addition of pembrolizumab in this clinical study. 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. However, surgery followed by RT ± cisplatin is SoC for participants with LA HNSCC. Pembrolizumab (Keytruda®) has been approved by the FDA for recurrent/metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

This study will assess the safety and efficacy of pembrolizumab used as neoadjuvant treatment prior to surgical resection and as adjuvant treatment in combination with RT ± cisplatin in participants with previously untreated resectable LA HNSCC. The benefit of pembrolizumab as neoadjuvant and adjuvant therapy in this specific patient population is unknown.

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

4 OBJECTIVES/HYPOTHESES AND ENDPOINTS

All objectives and hypotheses apply to male/female adult participants (≥18 years of age) with resectable LA HNSCC.

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 5.4.1.1.3 for further details.

Objective/Hypothesis	Endpoint
Primary	
• Objective 1: To compare pembrolizumab as neoadjuvant therapy and in combination with radiotherapy (RT) ± cisplatin as adjuvant therapy to only RT ± cisplatin as adjuvant therapy with respect to EFS per RECIST 1.1 as assessed by BICR in participants whose tumors express PD-L1 CPS≥10, CPS≥1, and in all participants regardless of CPS status. - Hypothesis #1: Pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy after surgical resection is superior to SoC surgical resection followed by RT ± cisplatin adjuvant therapy with respect to EFS per RECIST 1.1 by BICR in participants whose tumors express PD-L1 CPS≥10. - Hypothesis #2: Pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy after surgical resection is superior to SoC surgical resection followed by RT ± cisplatin adjuvant therapy with respect to EFS per RECIST 1.1 by BICR in participants whose tumors express PD-L1 CPS≥1. - Hypothesis #3: Pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy after surgical resection is superior to standard of care (SoC) surgical resection followed by RT ± cisplatin adjuvant therapy with respect to EFS per RECIST 1.1 by BICR in all participants.	• EFS – time from the date of randomization to the date of first record of any of the following events: radiographic disease progression (exceptions specified in Section 10.4.1.1), radiographic disease progression during the neoadjuvant phase that precludes surgery, local or distant disease progression or recurrence as assessed with imaging or biopsy as indicated, death due to any cause; a secondary primary malignancy is not considered an EFS event

Objective/Hypothesis	Endpoint
Secondary	
• Objective 2: To compare pembrolizumab neoadjuvant therapy to no neoadjuvant therapy with respect to the rate of major pathological response (mPR) as assessed by the central pathologist at the time of definitive surgery in participants whose tumors express PD-L1 CPS≥10, CPS≥1, and in all participants regardless of CPS status. - Hypothesis #4: Pembrolizumab neoadjuvant therapy is superior to no neoadjuvant therapy with respect to rate of mPR at the time of surgery in participants whose tumors express PD-L1 CPS≥10. - Hypothesis #5: Pembrolizumab neoadjuvant therapy is superior to no neoadjuvant therapy with respect to rate of mPR at the time of surgery in participants whose tumors express PD-L1 CPS≥1. - Hypothesis #6: Pembrolizumab neoadjuvant therapy is superior to no neoadjuvant therapy with respect to rate of mPR at the time of surgery in all participants.	• mPR – having less than or equal to 10% invasive squamous cell carcinoma within the resected primary tumor specimen and all sampled regional lymph nodes

Objective/Hypothesis	Endpoint
• Objective 3: To compare pembrolizumab as neoadjuvant therapy and in combination with radiotherapy (RT) ± cisplatin as adjuvant therapy to only RT ± cisplatin as adjuvant therapy with respect to OS in participants whose tumors express PD-L1 CPS≥10, CPS≥1, and in all participants regardless of CPS status. - Hypothesis #7: Pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy after surgical resection is superior to SoC surgical resection followed by RT ± cisplatin adjuvant therapy with respect to OS in participants whose tumors express PD-L1 CPS≥10. - Hypothesis #8: Pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy after surgical resection is superior to SoC surgical resection followed by RT ± cisplatin adjuvant therapy with respect to OS in participants whose tumors express PD-L1 CPS≥1. - Hypothesis #9: Pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy after surgical resection is superior to SoC surgical resection followed by RT ± cisplatin adjuvant therapy with respect to OS in all participants.	• OS – time from the date of randomization to the date of death due to any cause

Objective/Hypothesis	Endpoint
• Objective 4: To evaluate the rate of pathological complete response (pCR) as assessed by the central pathologist at the time of definitive surgery in participants whose tumors express PD-L1 CPS≥10, CPS≥1, and in all participants regardless of CPS status.	• pCR – having no residual invasive squamous cell carcinoma within the resected primary tumor specimen and all sampled regional lymph nodes
• Objective 5: To evaluate global health status/quality of life (QoL) and physical functioning scores using the European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire (QLQ)-C30, and swallowing, speech and pain symptoms using the EORTC Head and Neck–Specific QoL questionnaire (EORTC QLQ-H&N35) in participants whose tumors express PD-L1 CPS≥10, CPS≥1, and in all participants regardless of CPS status.	• EORTC QLQ C30- global health status/QoL scales (items 29 and 30) • EORTC QLQ-C30 physical functioning scales (items 1-5) • EORTC QLQ-H&N35 swallowing multi-item scale (items 35-38), speech multi-item scale (items 46, 53-54), and pain multi-item scale (items 31-34)
• Objective 6: To determine the safety and tolerability of pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy.	• AEs • Study drug discontinuations due to AEs
Exploratory	
• Objective 7: To compare pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy to only RT ± chemotherapy as adjuvant therapy, with respect to: - Local Regional Control - Distant Metastases-Free Survival (DMFS) - Incidence of second Head and Neck and Other Cancers	• Local regional control - time from date of randomization to the date of first record of radiographic disease progression (exceptions specified in Section 10.4.1.1), local recurrence as assessed with imaging or biopsy as indicated • DMFS - time from date of randomization to the date of first record of appearance of distant metastasis or death due to any cause • Number of second Head and Neck and Other Cancers

Objective/Hypothesis	Endpoint
• Objective 8: To compare EFS and OS between participant who receive pembrolizumab neoadjuvant therapy and pembrolizumab with RT ± cisplatin as adjuvant therapy and participants who receive only RT ± cisplatin as adjuvant therapy in: - High risk participants - Low risk participants	• EFS –time from the date of randomization to the date of first record of any of the following events: radiographic disease progression (exceptions specified in Section 10.4.1.1), radiographic disease progression during the neoadjuvant phase that precludes surgery, local or distant progression or recurrence as assessed with imaging or biopsy as indicated, death due to any cause, a secondary primary malignancy is not considered an EFS event • OS –time from date of randomization to date of death due to any cause
• Objective 9: To characterize health utilities in participants whose tumors express PD-L1 CPS≥10, CPS≥1, and in all participants regardless of CPS status	• EuroQol-5 dimensions (EQ-5D-5L)
• Objective 10: To identify molecular (genomic, metabolic and/or proteomic) biomarkers (eg, PD-L1 IHC, gene expression profiling etc) that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab used as neoadjuvant and in combination with RT ± chemotherapy as adjuvant. • Objective 11: To evaluate correlation of clinical response (mPR/pCR and survival) to tumor/ circulating markers at Screening and after treatments.	• The relationship between baseline biomarkers and clinical activity will be assessed by evaluating molecular (genomic, metabolic and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue. The relationship between baseline biomarkers and clinical activity will be assessed by evaluating biomarkers and their association with mPR, pCR, EFS and OS.

Objective/Hypothesis	Endpoint
• Objective 12: To compare pembrolizumab as neoadjuvant therapy and in combination with radiotherapy (RT) ± cisplatin as adjuvant therapy to only RT ± cisplatin as adjuvant therapy with respect to mPR, EFS, and OS in participants whose tumors express CPS ≥ 50.	• mPR – having less than or equal to 10% invasive squamous cell carcinoma within the resected primary tumor specimen and all sampled regional lymph nodes • EFS –time from the date of randomization to the date of first record of any of the following events: radiographic disease progression (exceptions specified in Section 10.4.1.1), local or distant progression or recurrence, as assessed with imaging or biopsy as indicated, death due to any cause • OS –time from date of randomization to date of death due to any cause
• Objective 13: to compare pembrolizumab as neoadjuvant therapy and in combination with radiotherapy (RT) ± cisplatin as adjuvant therapy to only RT ± cisplatin as adjuvant therapy on the rate of in situ carcinoma/dysplasia observed in surgically resected specimens.	• The presence of in situ carcinoma or dysplasia present in any of the surgically resected specimens from the primary tumor site and/or neck lymph nodes.

The study is considered to have met its objective if pembrolizumab is superior to SoC with respect to EFS at either its interim analysis (IA) or the final analysis (FA).

5 STUDY DESIGN

5.1 Overall Design

This is a Phase III, randomized, active-controlled, multisite, open-label study of pembrolizumab as neoadjuvant therapy and pembrolizumab in combination with SoC RT with/without cisplatin as post-surgical adjuvant therapy in treatment naïve participants with newly diagnosed Stage III/IVA, resectable LA HNSCC. The study will be conducted in conformance with Good Clinical Practices (GCP).

714 participants will be enrolled in the study, which will result in approximately 65% (~462) participants whose tumors express PD-L1 CPS≥10 and approximately 95% (~680) participants whose tumors express PD-L1 CPS≥1, randomized in a 1:1 ratio to:

- Treatment Arm A/pembrolizumab: Pembrolizumab (2 cycles) as neoadjuvant therapy followed by surgical resection followed by adjuvant therapy with pembrolizumab (15 cycles) plus SoC RT ± cisplatin.
- Treatment Arm B/SoC: No neoadjuvant therapy prior to surgical resection and adjuvant therapy with SoC RT ± cisplatin (see Figure 1).

Participants will be stratified by primary tumor site (oropharynx/oral cavity vs. larynx vs. hypopharynx), tumor stage (III vs. IVA), and PD-L1 status (TPS≥50% vs. TPS<50%). Stratification factors are described in Section 7.3.1.

A participant's HNSCC status for eligibility at Screening will be based on investigator assessment in accordance with the inclusion/exclusion criteria described in Section 6.1 – Inclusion Criteria and 6.2 – Exclusion Criteria. A formalin-fixed paraffin-embedded (FFPE) tumor tissue sample or slides obtained at a participant's initial diagnosis will be submitted to a designated central laboratory for PD-L1 status determination and for retrospective translational research.

Presurgery neoadjuvant treatment in the pembrolizumab arm (Arm A) should begin within 3 days of randomization or as close as possible to that date on which the participant is allocated or assigned. The timeframe for surgery (after the presurgery visit) is within 6 weeks (±10 days) after randomization. Participants in Arm A are allowed to proceed to surgery outside of this timeframe if the delays are due to an AE. Participants with delays other than for an AE may be considered with Sponsor consultation.

Participants in the SoC control arm (Arm B) will receive no neoadjuvant and will proceed directly to surgery as per local practice.

In both the pre- and post-operative treatment periods in Arm A, pembrolizumab will be administered IV 200 mg fixed dose Q3W; treatment will begin on Day 1 of each 3-week dosing cycle. Note: the required screening period and neoadjuvant treatment in Arm A are not expected to cause excessive delays in receipt of SoC surgery and post-surgical treatment, since surgery and RT require institutional planning and quality assurance (QA) procedures, as described in the Radiation Therapy Quality Assurance (RT QA) manual.

All participants in the pembrolizumab arm (Arm A) will have an imaging assessment prior to surgery at Week 6 (± 10 days). In the SoC arm (Arm B), the screening image will serve as the presurgery imaging. If the presurgery scans in Arm A or baseline scans in Arm B were done > 14 days prior to the date of surgery, then repeat imaging is required prior to surgery. All imaging assessments will be submitted for BICR. All participants will undergo a potentially curative surgical resection performed as part of the local SoC. A thorough evaluation of tumor status, pathological staging per AJCC Cancer Staging Manual (8th edition) and assessment of surgical margins and extranodal extension will be performed by

the local pathologist on all the tissues removed during the surgery. Resected surgical specimens will be submitted to the designated central laboratories for blinded pathological response assessment, determination of high risk pathologic features and translational research as described in Section 9 –Study Assessment and Procedures. A final and optional biopsy will also be performed at the time of recurrence, if applicable, for participants who agree to participate.

Adjuvant treatment will start when participants have recovered adequately from the morbidity and/or complications from the surgery and is recommended within 6 weeks of surgery. For adjuvant treatment, participants considered high-risk for recurrence (ie, positive margins [< 1 mm] or extranodal extension [defined as extension of SCC from within a lymph node through the fibrous capsule and into the surrounding connective tissue] in the surgical specimen), will receive RT plus concurrent cisplatin (3 cycles of 100 mg/m^2 Q3W) plus pembrolizumab (15 cycles of 200 mg Q3W) in the pembrolizumab arm (Arm A) and without pembrolizumab in the SoC arm (Arm B); participants considered lower risk for recurrence (ie, without positive margins or extranodal extension following surgical resection) will receive RT plus pembrolizumab (15 cycles of 200 mg Q3W) in the pembrolizumab arm (Arm A) and without pembrolizumab in the SoC arm (Arm B). Participants in the pembrolizumab arm may start pembrolizumab adjuvant treatment before starting RT ± cisplatin.

Participants who do not undergo surgical resection as originally planned, or have incomplete resection (ie, gross disease left behind) may receive salvage RT plus cisplatin ± pembrolizumab, depending on the assigned treatment arm. These participants may receive a total dose of RT up to 70 Gy and up to 3 cycles of cisplatin.

All participants will have post-RT imaging performed 12 weeks (± 7 days) after the end of RT ± cisplatin treatment and then every 3 months (91 ± 7 days) until the end of Year 3, the imaging schedule may then be reduced to every 6 months (182 ± 14 days) up to the end of Year 5. If an unplanned imaging assessment is performed before the first scheduled post-RT imaging and a disease progression is assessed per RECIST 1.1 and verified by BICR, this will be an EFS event. Participants who do not undergo the planned surgery, for whatever reason, will be followed by imaging assessments at the same time intervals from last dose of post-operative radiotherapy. Imaging scans will be performed until a primary efficacy endpoint event is observed for a participant (see Section 10.4 Analysis Endpoint for the definition of a primary efficacy analysis event).

Participants that display disease recurrence or have an event/progression and subsequently receive any anticancer treatment not specified in the protocol will discontinue study treatment and enter follow-up; any treatment would be considered post-study anticancer treatment.

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

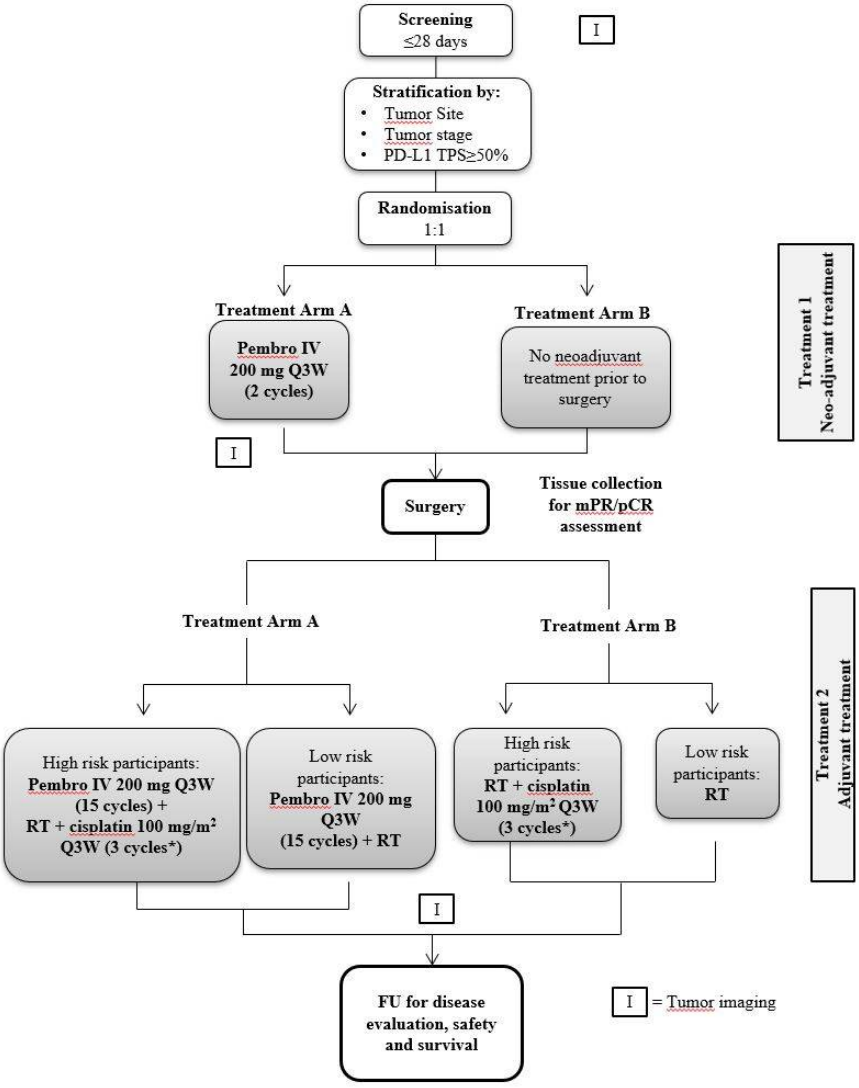
Safety follow-up will be performed for participants who receive study treatment and for those with Early Discontinuations. All participants will be followed for OS until death, withdrawal of consent, or the end of the study.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial SoA - Section 2. Details of each procedure are provided in Section 9 – Study Assessments and Procedures.

This study will use an independent, external Data Monitoring Committee (eDMC) and an Executive Oversight Committee to monitor safety and efficacy. There will be 2 formal IA for efficacy. These are detailed in Appendix 3 and Section 10.7.

5.1.1 Study Diagram

The study design is depicted in Figure 1.



*If there are delays in cisplatin treatment, cisplatin may continue for up to 1 week following completion of RT.

FU = follow-up; IV = intravenous; mPR = major pathological response; pCR = pathological complete response; PD-L1 = programmed cell death ligand 1; Pembro = pembrolizumab; Q3W = every 3 weeks; RT = radiotherapy; TPS = tumor proportion score.

Figure 1 Study Design

5.2 Number of Participants

In this study, 714 participants will be randomized as described in Section 10.9. Given the prevalence of PD-L1 positivity in tumors of patients with R/M HNSCC enrolled on KN048 and KN040 studies, it is expected that approximately 462 out of 714 participants enrolled in this study will have tumors with PD-L1 positive expression of CPS≥ 10 and approximately 680 participants whose tumors express PD-L1 CPS≥1.

5.3 Beginning and End of Study Definition

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

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory 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.

5.3.1 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.

5.4 Scientific Rationale for Study Design

A current SoC treatment regimen for newly diagnosed Stage III/IV resectable LA HNSCC consists of surgical resection of the tumor and involved lymph nodes, followed by either RT alone or in combination with cisplatin (100 mg/m^2 Q3W) based on the presence of high risk pathologic features of extranodal extension or positive margins [National Comprehensive Cancer Network 2017] [Cooper, J. S., et al 2004] [Bernier, J., et al 2004].

Around 50% of HNSCC are diagnosed at a locally advanced stage. The 5-year OS rate of HPV-negative Stage III/IV HNSCC remains low (40 to 60%). Participants with HPV-positive oropharyngeal cancer have a better prognosis, with the exception of participants with T4 or N3 disease for which the 5-year OS is around 50 to 60% (independently of their age and smoking status) [Huang, S. H., et al 2015].

Recurrent/metastatic HNSCC has potentially devastating impacts on basic functions such as eating, swallowing, speaking and breathing. In addition, the pain associated with recurrence, and the social isolation as well as potential disfigurement from the disease in the head/neck region, all point to the value of preventing progression in this potentially devastating disease. Furthermore, the prognosis of R/M HNSCC is poor with a median overall survival of under 1 year. There is thus an unmet medical need to support the development of new treatment strategies to improve the outcome of patients with newly diagnosed Stage III/IV LA HNSCC.

Immune checkpoints that regulate the immune response have led to the development of strategies that can be positively exploited to impact T-cell activity and generate clinically relevant antitumor activity. Pembrolizumab was granted accelerated approval for

participants with recurrent/metastatic HNSCC with disease progression on or after platinum-containing chemotherapy by FDA on 05-Aug-2016. The efficacy of pembrolizumab in other indications is summarized in the Investigator's Brochure.

Based on the potential to improve responses in patients with combination therapy that can activate different mechanisms of action, pembrolizumab is being evaluated in a number of combinations.

This study is designed to evaluate pembrolizumab as neoadjuvant therapy (presurgery) and pembrolizumab in combination with RT ± cisplatin (post-surgery) for Stage III-IVA resectable LA HNSCC. Pembrolizumab has shown significant clinical anticancer activity in recurrent/metastatic HNSCC (see Section 3.2.3).

Neoadjuvant treatment is an important part of the treatment strategy for locally advanced triple negative breast cancer and non-small cell lung cancer (NSCLC), both demonstrating a positive and significant correlation of pCR with long-term clinical benefit such as EFS and OS [Francisco, L. M., et al 2010].

The aim of presurgical neoadjuvant therapy in LA HNSCC is to shrink the tumor, increase rate of pCR and thus increase locoregional control with the potential to impact survival.

An initial Phase II MISP study (NCT02296684) [Uppaluri, R., et al 2017] of pembrolizumab has been initiated to evaluate the efficacy and safety of pembrolizumab as neoadjuvant therapy. In preliminary analysis of 21 participants who had received pembrolizumab 2 weeks prior to resection of high-risk (Stage IVA) LA HNSCC, nearly half (48%) demonstrated downstaging in pathologic sample resulting in 38% participants with high risk features (vs. expected 80%). Tumor shrinkage (>10%) in pathological samples was observed in 43% of participants with 6/21 (29%) having pathological treatment effect in ≥70% of the resected tissue area. No participants experienced recurrence, metastases, or death from disease (range of follow-up 3 to 18 months, half the participants had >12 months follow-up) and the post-operative treatment recommendation for CRT were altered (de-intensified). This Phase III study will seek to confirm these efficacy results in a larger population.

Pre-clinical investigations, as well as initial clinical observations provide a strong rationale for testing RT and cisplatin as potentiators of immune checkpoint inhibitors. The abscopal effect refers to a phenomenon of tumor regression at a site distant from the primary site of RT. Following the report of an abscopal effect in a participant with metastatic melanoma treated with RT and ipilimumab, interest in potential synergistic treatment combining radiation and immunotherapy have emerged [Postow, M. A., et al 2012]. A series of preclinical experiments have further developed the rationale for such combinations. RT has been combined with inhibitors of PD-1/PD-L1 pathway in various murine models (melanoma, breast, glioblastoma, colon) with an improvement in the tumor growth control and survival of the mice compared to single treatment modality [Sharabi, A. B., et al 2015] [Zeng, J., et al 2013].

Recent evidence has shown that besides their effects on DNA, RT and chemotherapy induce immunomodulatory effects that could contribute to their therapeutic efficacy. Both have the

potential to overcome some of the mechanisms of tumor immune escape [Machiels, J. P., et al 2001].

Radiotherapy used at therapeutic doses as well as some cytotoxic agents induce immunogenic cell death and the release of tumor antigens that can effectively prime antigen presenting cells. Radiotherapy and chemotherapy act on the microenvironment to decrease its immunosuppressive properties by inducing the release of cytokines and chemokines that have the ability to attract T-cells [Golden, E. B. 2015]. In addition, RT may augment the tumor-infiltrating lymphocytes numbers and broaden their T-cell receptor repertoire [Derer, A., et al 2016] [Esposito, A., et al 2015] of cytotoxic effectors cells [de Biasi, A. R., et al 2014]. RT also increases the expression of PD-L1 on tumor cells, which can also explain part of the synergism [Deng, L., et al 2014].

The effects of RT and chemotherapy on the immune system are a dynamic process. A lot of uncertainties remain in regard to the optimal dose, sequencing and timing of each modality to use but results of the current study will certainly contribute to improve our knowledge in this field.

There is a need to identify new treatment strategies that can increase the efficacy of CRT particular in patients considered at high risk of recurrence post-surgical resection. Preclinical studies investigating the sequence of PD-1 immunotherapy in relationship to CRT have not been well studied. However, preclinical studies suggesting the importance of immune priming would support the notion that administering pembrolizumab prior to CRT may be important. In this study, pembrolizumab will be used as neoadjuvant and an add-on to SoC RT ± cisplatin adjuvant therapy post-surgical resection in an arm of randomized LA HNSCC participants. Pembrolizumab will be given concurrently with RT ± cisplatin and continued as maintenance (total duration of pembrolizumab treatment approximately 1 year). The control SoC treatment arm will receive SoC surgery followed by RT ± cisplatin adjuvant therapy.

An initial Phase II MISP study of pembrolizumab in combination with CRT for LA HNSCC has been initiated to evaluate the safety and tolerability of pembrolizumab combined with cisplatin and RT (NCT02296684) [Uppaluri, R., et al 2017]. Currently, this study has enrolled 25 out of 46 participants. Treatment consists of a loading dose of pembrolizumab 200 mg IV given 7 days prior to initiation of CRT and continued Q3W during CRT and following completion of CRT for a total of 8 doses. Chemoradiotherapy is administered in this MISP study using weekly cisplatin treatment followed by additional pembrolizumab. Thus far, the combination does not appear to show significant changes compared to standard CRT in terms of toxicity, but a formal analysis of toxicities has not yet been done. The efficacy and safety of pembrolizumab in combination with RT plus cisplatin, in unresectable LA HSNCC, is currently under further investigation in the ongoing Phase III study KN412 (see Section 3.2.3).

5.4.1 Rationale for Endpoints

5.4.1.1 Efficacy Endpoints

5.4.1.1.1 Major Pathological Response

Although OS is the standard endpoint for Phase 3 oncology studies, using this primary endpoint in studies in primary resectable HNSCC would require a decade or longer to complete, slowing patient access to potential new therapies. In this study, mPR defined as having less than or equal to 10% invasive squamous cell carcinoma within the resected primary tumor specimen and all sampled regional lymph nodes, is being used as a predictive endpoint of long-term survival, in LA HNSCCs treated with neoadjuvant pembrolizumab, and can be measured closer to the post-surgical window rather than waiting for the accrual of OS events.

In breast cancer, pCR rate has been used as an endpoint in numerous studies of neoadjuvant systemic therapy and is a well-established predictive endpoint for FDA registration based on currently approved systemic neoadjuvant therapy in breast cancer. However, the achievement of pCR can be rare in other cancers, which may restrict its use as a predictive endpoint. Thus researchers have evaluated less restrictive definitions of pathological response after neoadjuvant chemotherapy, including mPR. In lung cancer, whereas median pCR rate reported from studies of neoadjuvant chemotherapy is 4% (range 0 to 16%), mPR rate is approximately 22%, establishing that the endpoint is sufficiently frequent to allow statistically relevant assessments with reasonable sample sizes [Hellmann, M. D., et al 2014]. Across published lung cancer study of neoadjuvant systemic therapy, mPR rate has been demonstrated to be a consistently valid predictive endpoint for OS establishing the clinical relevance of this endpoint [Hellmann, M. D., et al 2014] [Pataer, A., et al 2012].

Consistent with this observation, prior literature in resectable locoregionally advanced oral cavity HNSCC has also identified significant long term survival benefit for individual patients who attain mPR. In a randomized study of neoadjuvant chemotherapy versus SoC surgery, Zhong et al. (2015) identified that patients who achieved mPR (28%) with neoadjuvant chemotherapy had a more than 80% 5-year OS rate [Zhong, L. P., et al 2015]. The mPR rate was associated with statistically significant improvement in 5-year OS both in comparison with patients in the neoadjuvant treatment arm who did not achieve mPR (hazard ratio [HR] =0.37, 95% CI: 0.15, 0.87, p=0.023) and in comparison with SoC surgery (HR=0.35, 95% CI: 0.15, 0.82, p=0.014). These comparisons were also statistically significant for the 5-year disease free survival, locoregional recurrence-free survival, and DMFS endpoints.

5.4.1.1.2 Pathological Complete Response

Pathological complete response, defined as no residual invasive squamous cell carcinoma within the resected primary tumor specimen and all sampled regional lymph nodes, is associated with a reduced risk of recurrent/metastatic disease and in this study is being used as a surrogate of survival in LA HNSCCs treated with neoadjuvant pembrolizumab.

In breast cancer, patients who achieve pCR using systemic therapy have demonstrated sustained clinical benefit with significant improvements in survival for individual patients who attain pCR [Carey, L. A., et al 2007] [Liedtke, C., et al 2008] [Cortazar, P., et al 2014]. In this study, pCR is included as a secondary endpoint because the achievement of pCR can be rare in other cancers, which may restrict its use as a predictive endpoint.

In resectable Stage II-IV local or locoregionally advanced oral cavity HNSCC, a randomized control study of neoadjuvant chemotherapy found that patients with a pCR (27%) had a significant survival improvement when compared with those without a pCR (10-year OS: 76% vs. 41%, p=0.0004; HR 0.23) [Bossi, P., et al 2014]. The benefit in survival mainly depended on better locoregional control of disease: the crude cumulative incidence of locoregional recurrence at 10 years was 11.1% for patients achieving a pCR, while was 33% for patients with residual disease after chemotherapy (p=0.029). Notably, patients who achieved a pCR with neoadjuvant chemotherapy had a relatively less advanced stage at diagnosis, with 41% Stage II, 50% Stage III and 9% Stage IV disease, highlighting the rarity of pCR achieved in the Stage III-IV population to be studied in the proposed study of pembrolizumab.

5.4.1.1.3 Event-Free Survival

Event-free survival is a common surrogate endpoint for OS that is used to evaluate the efficacy of neoadjuvant and adjuvant cancer therapy and is sometimes used as primary endpoint. In this study, EFS does not include a pathologic component and rather defines a presurgical radiographic event as a progression that precludes surgery. This is to align with the ongoing and recently completed neoadjuvant trials across disease types. These trials notably do not contain pathologic cutoffs in the definition of an event [NCT: 03221426, NCT: 03924895, NCT: 03425643, NCT: 03924856] [Patel, S. P., et al 2023] [Schmid, P., et al 2020] [Forde, P. M., et al 2022]. Additionally, emerging concepts and pathologic response data among the neoadjuvant HNSCC clinical landscape have demonstrated a survival benefit among a broader population of pathologic responders, expanded beyond the strict definitions of mPR and pathologic complete response (pCR; 0% remaining invasive cancer) [Menzies, A. M., et al 2021] [Wise-Draper, T. M., et al 2022] [Uppaluri, R., et al 2020] [Dogan, S. 2023] [Topalian, S. L., et al 2020]. See Section 10.4 for the primary and secondary endpoint definitions.

Event-free survival represents a clinically significant endpoint for patients with this disease, given the morbidity associated with recurrent HNSCC and its potentially devastating impact on basic functions such as eating, swallowing, speaking and breathing. The use of BICR and RECIST 1.1 to assess disease progression is typically considered acceptable by regulatory authorities. RECIST 1.1 will be used by the BICR when assessing images for efficacy measures and by the local site when determining eligibility (Section 9.2.1.4). Although traditional RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented a modification to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ. Images will be read by a central imaging vendor blinded to treatment assignment to minimize bias in the response assessment. In addition, the final determination of radiologic progression will be based on the central assessment of progression, rather than a local site investigator/radiology assessment. Real time

determination of radiologic progression as determined by central review will be communicated to the site.

The recent clinical study results of PD-1 inhibitors in the recurrent or metastatic HNSCC setting points to the likelihood of their wide-spread availability in the near future. Thus their use in the recurrent setting will likely impact the OS endpoint, as participants who are randomized to the SoC control arm (Arm B) may subsequently receive a PD-1 inhibitor at recurrence.

5.4.1.1.4 Overall Survival

Overall survival has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies. In this study, OS will be measured as a key secondary endpoint. The OS endpoint may be potentially confounded by subsequent therapy, thus limiting its utility as a primary endpoint. For example, the impact of unintended cross-over from approval of PD-1 inhibitors in the recurrent/metastatic HNSCC setting will likely result in wide-spread availability and usage of PD-1 inhibitors in the near future. Their use in the recurrent setting will likely impact the OS endpoint, as participants who are randomized to the SoC control arm may subsequently receive a PD-1 inhibitor at recurrence due to their approved usage in the recurrent setting. Also, the OS endpoint for this disease can be heterogeneous given the variability of salvage procedures, which is highly center and expertise dependent, and this variability may have an impact on the OS endpoint. Further complicating the OS endpoint is that participants who survive more than 2 to 3 years have an OS impact mainly driven by participant co-morbidities and second primaries, rather than by disease recurrence. For all the reasons stated above, EFS is the primary endpoint and OS will be a secondary endpoint.

5.4.1.1.5 Rationale for Prospective Stratification and Evaluation of Biomarker Subpopulation

Studies in additional indications (melanoma and lung) suggest that participants respond to pembrolizumab even if their tumors show little or no PD-L1 by IHC, although potentially at a lower rate of response than when tumors are more positive for PD-L1. In R/M HNSCC, KEYNOTE-012 participants in Cohort B were evaluated to determine whether participants whose tumors express PD-L1 participants are more likely to demonstrate higher ORRs than anticipated for participants whose tumors do not express PD-L1 (see Section 3.2.3). In a pooled analysis, higher response rates were observed in patients with PD-L1 versus without PD-L1 expression using CPS≥ 1 (21% vs. 6%; one-sided $P = 0.023$) [Mehra, R., et al 2018].

In addition, data from KEYNOTE-040 demonstrated a survival benefit with higher PD-L1 expression for pembrolizumab relative to SoC when PD-L1 expression is higher on tumors and in the tumor microenvironment [Cohen, E. E. W., et al 2019]. The hazard ratio (HR) for OS for both participants with PD-L1 CPS ≥ 1 (HR 0.74, nominal p=0.0049) and TPS ≥ 50% (HR 0.53, nominal p=0.0014) demonstrated the benefit of pembrolizumab compared with SoC in KEYNOTE-040. Data from KEYNOTE-048 showed that pembrolizumab significantly improved OS in both the PD-L1 CPS ≥ 20 (HR 0.61 [95% CI 0.45-0.83],

p=0.0007), and CPS ≥ 1 (HR 0.78, *p*=0.0086) populations compared to the EXTREME regimen, supporting pembrolizumab monotherapy for 1L treatment of PD-L1 positive R/M HNSCC [Burtness, B., et al 2018].

Based on these results observed in first-line and second-line R/M HNSCC, it is reasonable to expect that biomarker enrichment effects are also likely to be seen in locally advanced HNC. Most recently, in post hoc analysis of KEYNOTE-412, a numerically improved survival benefit was demonstrated in the CPS≥10 (EFS HR=0.73, CI: 0.53-1.02; OS HR=0.72, CI: 0.50-1.04) and CPS≥20 populations (EFS HR=0.73, CI: 0.49-1.06; OS HR=0.67, CI: 0.43-1.04) that was not similarly observed in a CPS unselected (OS HR=0.90; CI: 0.71-1.15) or CPS≥1 populations (EFS HR=0.80, CI: 0.64-1.00; OS HR=0.88, CI: 0.68-1.14) [Machiels, J. P., et al 2022] [Rugo, H. S., et al 2022].Therefore biomarker-driven hypotheses for efficacy endpoints will be assessed in this study and the selected populations for analysis will be CPS≥10, CPS≥1, and all participants.

Further details of the statistical approach to evaluating this population are described in Section 10.5.1. In addition, to safeguard against differences in allocation of subjects with TPS ≥ 50%, subjects will be stratified based on their TPS.

5.4.1.2 Safety Endpoints

The safety objective of this study is to evaluate the safety of pembrolizumab used as neoadjuvant and as an adjuvant in combination with RT ± cisplatin in participants with resectable LA HNSCC. Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/ SAEs; and changes in vital signs and laboratory values. Adverse events will be assessed as defined by CTCAE, Version 4.0. The severity (as CTCAE grade), attribution to drug, time-of-onset, duration, resolution and any concomitant medications administered will be recorded.

5.4.1.3 Rationale for Patient Reported Outcomes (PROs)

As part of the analyses for this study, participants will provide information regarding their health-related quality of life using the EORTC QLQ-C30 and EORTC-QLQ-H&N35 patient reported outcome (PRO) instruments. Health utilities will be evaluated using the EuroQol-5D (EQ-5D-5L) PRO instrument. These PRO assessments are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

EORTC QLQ-C30 and EORTC QLQ-H&N35

The EORTC QLQ-C30 is the most widely used cancer specific health related QoL instrument, which contains 30 items and measures 5 functional dimensions (physical, role, emotional, cognitive and social), 3 symptom items (fatigue, nausea/vomiting, and pain), 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].

The EORTC QLQ-H&N35 is a disease specific questionnaire developed to measure QoL in HNC. 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].

The EORTC QLQ-C30 and EORTC QLQ-H&N35 are psychometrically and clinically validated instruments appropriate for assessing QoL in participants with HNCs [Bjordal, K., et al 1994] [Bjordal, K., et al 2000]. These instruments have been widely used in Phase 3 studies of participants with locoregionally advanced HNSCC [van Herpen, C. M., et al 2010] [Bottomley, A., et al 2014] [Curran, D., et al 2007].

Clinically meaningful symptoms for HNSCC patients have been extensively studied, and commonly identified symptoms include: problems with swallowing, problems with speech, and pain in the mouth [Bjordal, K., et al 2000] [Chera, B. S., et al 2014]. Thus, secondary objectives are to assess mean changes from baseline in the global health status/QoL and physical functioning scores from the EORTC QLQ-C30, as well as the above-mentioned symptom scores from the EORTC QLQ-H&N35. A difference of 10 points on the 100-point EORTC QLQ-C30 and EORTC QLQ-H&N35 scales either from baseline or between the cohorts is considered as clinically relevant [Bjordal, K., et al 1994] [Bjordal, K., et al 2000].

EuroQoL-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in health economic analyses [Rabin, R. and de Charro, F. 2001]. The 5 health state dimensions in the EQ-5D-5L include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 5-point scale from 1 (no problem) to 5 (unable to/extreme problems). The EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the participant rates 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].

5.4.1.4 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 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, as well as determinants of AEs in the course of our clinical studies. These efforts will identify novel predictive/pharmacodynamic biomarkers and generate information that will 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, single-nucleotide polymorphism [SNP] analyses, whole exome sequencing, whole genome sequencing):

This research will 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. Finally, MSI may be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer).

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 etc.). Key molecular changes of interest to immune-oncology drug development include (for example) 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. 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. Microsatellite instability may also be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer). 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 may also be evaluated (eg, IL-10). MicroRNA profiling may also be pursued.

Proteomics and immunohistochemistry 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 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. 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 therapy.

Other blood-derived biomarkers:

In addition to expression on the tumor tissue, PD-L1 and other tumor derived proteins can be shed from tumor and released into the blood. Assays such as enzyme-linked immunoassay measure such proteins in serum. Correlation of expression with response to pembrolizumab 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.

5.4.1.5 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens consented for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research are presented in Appendix 6 – Collection and Management of Specimens for Future Biomedical Research.

5.4.2 Rationale for the Use of Comparator

In this study, the comparator is SoC treatment. In clinical practice, there is no established neoadjuvant therapy for newly diagnosed LA HSNCC, as multiple Phase III studies have

been conducted using various chemotherapy regimens without an established standard. In this study, in the neoadjuvant period, treatment naïve participants will be treated with either pembrolizumab (Arm A) or no therapy before surgery (Arm B). A placebo is not being used in the neoadjuvant treatment period to avoid participant burden and delays in receipt of available recommended surgery/treatment in a high-risk population; participants randomized to no neoadjuvant therapy will go directly to surgery.

In the post-surgery (adjuvant) phase, all participants will be treated with SoC RT ± cisplatin. Treatment with cisplatin will be based on the local pathological assessment of the participant's surgical specimen and their risk for the development of recurrent/metastatic disease post-surgery. In clinical studies, pembrolizumab has demonstrated clinical anticancer activity in patients with recurrent/metastatic HNSCC and in this study its efficacy as an add-on to post-surgery SoC RT ± cisplatin in newly diagnosed HNSCC will be explored.

5.5 Justification for Dose

The planned dose of pembrolizumab for this study is 200 mg Q3W. Based on the totality of data generated in the Keytruda® development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. The fixed dose regimen of 200 mg Q3W is also in line with the approved labeling for recurrent/metastatic HNSCC with disease progression on or after platinum-containing chemotherapy. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure- efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W,
- Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically based pharmacokinetic [PBPK] analysis) at 200 mg Q3W.

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

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

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

5.5.1 Maximum Dose/Exposure for This Trial

Late responders have been observed with pembrolizumab up to 1 year of treatment in the recurrent/metastatic setting supporting the 1-year duration of treatment with pembrolizumab. Participants in Arm A will receive pembrolizumab 200 mg Q3W for up to 17 cycles in total.

6 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 3), our studies include people of varying age, race, ethnicity, and sex. The collection and use of these demographic data are to follow all local laws and guidelines in keeping with the needs for participant confidentiality while supporting the study of the disease, its related factors, and the IMP under investigation.

Male/Female participants with newly diagnosed Stage III or IVA resectable LA HNSCC of at least 18 years of age will be enrolled in this trial.

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

6.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Type of Participant and Disease Characteristics

1. Have histologically confirmed new diagnosis of resectable, non-metastatic, squamous cell carcinoma as assessed by the Investigator based on baseline imaging and clinical assessment that is either:
    a. Stage III oropharyngeal p16 positive that is T4 (N0-N2), M0
    OR

b. Stage III or IVA oropharyngeal p16 negative
OR

c. Stage III or IVA larynx/hypopharynx/oral cavity (independent of p16).

Note: Participants with multiple primary HNSCC tumors are eligible for the study if at least one of the tumors meets eligibility criteria based on staging after consultation with and approval by the Sponsor.

Note: If an excisional or incisional biopsy has been performed, participants remain eligible for the study provided the residual disease meets the staging criteria required for the study (eg, excisional biopsy of a lymph node with residual T4a primary).

Note: Prior surgical debulking, including tonsillectomy, for the head and neck cancer under study is not allowed.

2. Be eligible for primary surgery based on investigator decision and per local practice. This decision must be validated by members of a multidisciplinary team, including the surgical oncologist, medical oncologist and radiation oncologist.

Demographics

3. Male/female participants who are at least 18 years of age at the time of providing informed consent.

Male participants:

4. If male, agrees to the following during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The length of time required to continue contraception for each study intervention is as follows:
    - Pembrolizumab: no contraception requirement
    - Cisplatin: 180 days
    - Radiotherapy: 90 days
    - Refrains from donating sperm

PLUS either:

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

OR

- Uses contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview) as detailed below:
  - Uses a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.
  - Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

Female participants:

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

   - Not a WOCBP

OR

   - A WOCBP and:
     - Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The length of time required to continue contraception for each study intervention is as follows:
       - Pembrolizumab: 120 days
       - Cisplatin: 180 days
       - Radiotherapy: 180 days

     The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

- Has a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours for urine or within 72 hours for serum before randomization. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 9.5.9.2.
- Abstains from breastfeeding during the study intervention period and for at least 120 days after the last dose of pembrolizumab and 180 days after the last dose of cisplatin.
- Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

6. The participant (or legally acceptable representative) provides documented informed consent for the study. The participant may also provide consent for Future Biomedical Research. However, the participant may participate in the main study without participating in Future Biomedical Research.

Study Assessments

7. Have evaluable tumor burden (measurable and/or non-measurable tumor lesions) assessed by computed tomography (CT) scan or magnetic resonance imaging (MRI), based on RECIST 1.1 as assessed by the local site investigator/radiology.
8. Have provided newly obtained core or excisional biopsy of a tumor lesion not previously irradiated for central PD-L1 biomarker analysis from a core or excisional biopsy (fine needle aspirate [FNA] is not adequate) for stratification prior to randomization. Repeat samples may be required if adequate tissue is not provided. Formalin-fixed, paraffin embedded tissue blocks are preferred to slides.

   Note: If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory within 14 days from the date slides are cut (details pertaining to tumor tissue submission can be found in the Vendor Manual).
9. Have results from (local) testing of HPV status for oropharyngeal cancer defined as p16 IHC testing using CINtec® p16 Histology assay (Ventana Medical Systems Inc., Tucson AZ) using standard protocol. Positive p16 expression is defined as strong and diffuse nuclear and cytoplasmic staining in 70% or more of the tumor cells (please see Section 9.1.6 - Presurgery Tumor Tissue Collection for details). If HPV status was previously tested using this method, no additional testing is required.

   Note: HPV testing will be performed using local testing of HPV status in participants with oropharyngeal cancer using the specified method.

Note: If local p16 testing results are not available, or cannot be assessed locally by the specified method, a tumor tissue sample must 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 these tumor locations are assumed to be HPV-negative.

10. Have an ECOG performance status of 0 to 1 performed within 10 days of randomization.

    Note: Investigators to confirm no deterioration prior to initiation of treatment.

11. Have adequate organ function as defined in the following table (Table 1). Specimens must be collected within 10 days prior to randomization. If a screening lab does not meet eligibility criteria and is repeated and assessed on Day 1 and the Day 1 lab meets eligibility criteria, the participant is eligible, ie, the Day 1 lab result will be used for eligibility.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count	≥1500/μL
Platelets	≥100 000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L
Renal	
Measured or calculated[a] creatinine clearance (CrCl; glomerular filtration rate [GFR] can also be used in place of CrCl)	≥60 mL/min
Calcium (corrected for albumin)[c]	≤11.5 mg/dL or ≤2.9 mmol/L
Albumin	Result used to provide corrected calcium value only
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
Coagulation	
International normalized ratio (INR) or prothrombin time (PT) Activated partial thromboplastin time (aPTT) or Partial Thromboplastin Time (PTT)[b]	≤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] Cockcroft Gault calculation of CrCl preferred, but CrCl can be calculated per institutional standard. The formula used to calculate creatinine clearance should be the same and consistent for all participants at the site.

[b] PTT may be performed if the local lab is unable to perform aPTT.

[c] Calcium corrected for albumin is required during screening only for participants with albumin outside the normal range.

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.

6.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Has Stage T4B and/or N3 LA HNSCC and/or distant metastases.

   Note: As per the AJCC Cancer Staging Manual, 8th edition, the diagnosis of ENE (eg, N3b disease) requires clear evidence of gross ENE on clinical examination supported by strong radiographic evidence. Chapter 5, Staging Head and Neck Cancers, in the AJCC Cancer Staging Manual, 8th edition, defines criteria for evidence of gross ENE on clinical evaluation.
2. Has cancer outside of the oropharynx, larynx, and hypopharynx or oral cavity, such as nasopharyngeal, sinus, other para-nasal, or other unknown primary HNC.
3. A WOCBP who has a positive pregnancy test within 24 hours (urine) or within 72 hours (serum) before randomization or within 24 hours prior to the start of RT ± cisplatin (see Section 9.5.9.2). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

Prior/Concomitant Therapy

4. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).
5. Has received prior radiotherapy treatment or systemic anticancer therapy including investigational agents for the HNC under study prior to randomization/allocation.
   Note: Radiation therapy to treat a prior HNC is also grounds for exclusion.
6. Has received a live vaccine within 30 days prior to randomization. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist® [Influenza Vaccine Live, AstraZeneca]) are live attenuated vaccines and are not allowed.

   Refer to Section 7.7 for information on COVID-19 vaccines.

Prior/Concurrent Clinical Study Experience

7. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to randomization.

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

Diagnostic assessments

8. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to randomization.
9. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.

   Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, in situ cervical cancer or breast carcinoma) that have undergone potentially curative therapy are not excluded.
10. Has radiographically detectable (even if asymptomatic and/or previously treated) central nervous system metastases and/or carcinomatous meningitis as assessed by local site investigator and radiology review.
11. Has Grade ≥2 audiometric hearing loss.

    Note: Audiometric abnormalities without corresponding clinical symptoms of Grade ≥2 hearing loss will not be grounds for exclusion.

    Note: Participants with complete non-tumor-related hearing loss (ie, congenital deafness) are eligible for this study.
12. Has Grade ≥2 neuropathy.
13. Has Grade 3-4 bleeding due to the underlying malignancy.
14. If participant has received major surgery, and the participant has not recovered adequately from the toxicity and/or complications from the intervention prior to randomization.
15. Has had previous allogeneic tissue/solid organ transplant.
16. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients (refer to the Investigator's Brochure for a list of excipients), RT or cisplatin or their analogs.
17. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
18. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
19. Has an active infection requiring systemic therapy.
20. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority. Refer to Appendix 8 for Germany-specific requirements.

21. Has a known history of or is positive for Hepatitis B (defined as hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C (defined as Hepatitis C virus [HCV] RNA [qualitative] is detected). Refer to Appendix 8 for Germany-specific requirements.

    Note: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.
22. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
23. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

Other Exclusions

24. Removed in Amendment 07 for duplication of requirement with inclusion criteria #4 and #5.
25. Refer to Appendix 8 for additional France-specific exclusion criterion.
26. Refer to Appendix 8 for additional France-specific exclusion criterion.
27. Refer to Appendix 8 for additional France-specific exclusion criterion.

6.3 Lifestyle Restrictions

6.3.1 Meals and Dietary Restrictions

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

Insertion of feeding tube is allowed for nutritional purposes and, if procedure is performed as a planned hospitalization, would not meet that criterion for SAE.

6.3.2 Caffeine, Alcohol, and Tobacco

No caffeine, alcohol or tobacco restrictions are required.

6.3.3 Activity

No activity restrictions are required.

6.3.4 Contraception

Pembrolizumab, cisplatin, and RT may have adverse effects on a fetus in utero. Refer to Appendix 5 for approved methods of contraception. Refer to Appendix 8 for Germany-specific guidance.

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, participants of childbearing potential must adhere to the contraception requirement (Appendix 5) from the day of study medication initiation throughout the study period up to 120 days after the last dose of pembrolizumab (applicable for WOCBP only), 180 days after the last dose of cisplatin, and 90 days (males) or 180 days (WOCBP) after the last dose of radiotherapy. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

6.3.5 Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 9.3.6.

6.3.6 Use in Nursing Women

Pembrolizumab: It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, participants who are breastfeeding are not eligible for enrollment.

Cisplatin: Cisplatin has been reported to be found in human milk; participants receiving cisplatin injection should not breast-feed.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any adverse events or serious adverse events (SAE) meeting reporting requirements as outlined in the entry guidelines.

6.5 Participant Replacement Strategy

A participant who discontinues from study treatment or withdraws from the study will not be replaced.

7 TREATMENTS

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

Clinical supplies [study treatment(s) provided by the Sponsor] will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

7.1 Treatments Administered

The study treatment(s) to be used in this trial are outlined below in Table 2.

Refer to Appendix 8 for country-specific requirements.

Table 2 Study Treatment(s)

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP/ NIMP/ AxMP	Sourcing
Arm A	Experimental	Pembrolizumab	Drug	Solution for infusion	100 mg/vial	200 mg	IV infusion	Q3W for up to 17 cycles	Test Product	IMP	Central
Arm A	Experimental	Radiotherapy	Radiation	NA (Radiation)	2 Gy/fraction	2 Gy/day	Internal radiation - systemic	Low-risk participants: 2 Gy/day in 30 fractions for a total of 60 Gy High-risk participants: 2 Gy/day in 33 fractions for a total of 66 Gy Participants with gross residual disease: 2 Gy/day in 35 fractions for a total of 70 Gy	Background treatment	NIMP/ AxMP	Local
Arm A	Experimental	Cisplatin	Drug	Solution for infusion	1 mg/mL	100 mg/m^2	IV infusion	Q3W for 3 cycles	Test Product	IMP	Local or central
Arm B	Active comparator	Radiotherapy	Radiation	NA (Radiation)	2 Gy/fraction	2 Gy/day	Internal radiation - systemic	Low-risk participants: 2 Gy/day in 30 fractions for a total of 60 Gy High-risk participants: 2 Gy/day in 33 fractions for a total of 66 Gy Participants with gross residual disease: 2 Gy/day in 35 fractions for a total of 70 Gy	Background treatment	NIMP/ AxMP	Local

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admini-stration	Regimen/ Treatment Period	Use	IMP/ NIMP/ AxMP	Sourcing
Arm B	Active com-parator	Cisplatin	Drug	Solution for infusion	1 mg/mL	100 mg/m^2	IV infusion	Q3W for 3 cycles	Test Product	IMP	Local or central

Abbreviations: AxMP=auxiliary medicinal product; EEA =European Economic Area; IMP=investigational medicinal product; IV=intravenous; NA=not applicable; NIMP=noninvestigational medicinal product; Q3W=every 3 weeks.

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/NIMP/AxMP may exist. In these circumstances, local legislation is followed.

Pembrolizumab and cisplatin are allowed to be given on the same day.

Intensity modulated radiation therapy (IMRT) is mandatory. Dose is 60 Gy prescribed to at least 95% of the planning target volume (PTV). If image-guided radiation therapy (IGRT) is used, it should be daily to assure that error/variance is <3 mm. Dose-limiting normal tissue constraints are listed in Table 10.

Cisplatin will be provided locally in some countries by the study site, subsidiary or designee, depending on local country operational or regulatory requirements.

All supplies indicated in Table 2 will be provided per the 'Sourcing' row depending upon local country operational requirements. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

Refer to section 9.1.10 for details regarding administration of the study treatment.

All study treatments will be administered as per local SoC. Pembrolizumab may be administered on an out-patient basis; cisplatin will be prepared and administered as per the approved product labels.

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

7.2 Dose Modification (Escalation/Titration/Other)

If appropriate, the investigator may attribute each toxicity event to cisplatin, radiation or pembrolizumab alone and use a stepwise dose reduction according to Table 3 to Table 7. For individual participants requiring a dose modification, treatment for each new cycle may be delayed if the scheduled off-drug periods are not adequate to allow for recovery to Grade ≤1 or the baseline status of the participant. Every effort should be made to continue RT without interruption even in the case of pembrolizumab or cisplatin toxicity.

Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment should be interrupted or discontinued due to toxicity. If a dose reduction for toxicity occurs with cisplatin, the dose may not be re-escalated. Participants can have a maximum of 2 dose modifications throughout the course of the study for toxicities. If a participant experiences several toxicities and there are conflicting recommendations, please follow the most conservative dose adjustment recommended (dose reduction appropriate to the most severe toxicity).

If one or more of the study medications (ie, pembrolizumab, cisplatin and/or radiation therapy) is discontinued, the participant may continue with the other study medications if indicated. The last dose of cisplatin must be administered within 1 week of completion of RT as the chemoradiosensitizing effects will still be present.

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

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

If cisplatin and/or radiation therapy is discontinued, the participant may continue on treatment with pembrolizumab.

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

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 3.

Table 3 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

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

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Recurrent Grade 2 or Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST / ALT Elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [a]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [a]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or Permanently discontinue [a]		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue [b]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab monotherapy, coformulations or IO combinations may be resumed.

[b] Events that require discontinuation include, but are not limited to: Guillain-Barre Syndrome, encephalitis, myelitis, DRESS, SJS, TEN and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 4.

Table 4 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 pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500 to 1000 mg po (or equivalent dose of analgesic).

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

Abbreviations: CTCAE = Common Terminology Criteria for AEs; IV = intravenous; NCI = National Cancer Institute; NSAIDs = nonsteroidal anti-inflammatory drugs; po = per os; 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 CTCAE Version 4.0 at http://ctep.cancer.gov

Other allowed dose interruptions for pembrolizumab

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

7.2.2 Dose Modification for Radiotherapy

All RT treatments must begin as per planned SoC following recovery from surgery, as determined by the investigator. Ideally, this should be within 6 weeks of surgery. Treatment interruptions are to be avoided unless medically necessary. Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Treatment breaks, if necessary, ideally should not exceed 7 treatment days at a time and 14 treatment days total. Sites should consult the PI prior to giving any RT treatment breaks. Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and not for social or logistical reasons. Any treatment break(s) exceeding 2 treatment days for reasons other than toxicity/illness will be considered a protocol deviation.

Missed treatments should be compensated for with a twice a day treatment with minimum 6-hour inter-fraction interval to compensate for missed days including holidays and those for toxicity or illness once sufficiently recovered with the goal of keeping the overall treatment time confined to 6 weeks or 45 consecutive days. If BID treatments are not a part of local standard of care, RT should be continued until all 35 fractions are completed.

If cisplatin and/or pembrolizumab are discontinued, participants may stay on study treatment to complete radiation therapy.

7.2.3 Dose Modification for Cisplatin

Participants can have 2 levels of dose reductions of cisplatin throughout the course of the study for toxicities as described in Table 5.

If further toxicity occurs or the criteria for resuming treatment are not met, the participant must be discontinued from that drug and continue to participate in the study. If a participant experiences several toxicities and there are conflicting recommendations, follow the most conservative dose adjustment recommended (dose reduction appropriate to the most severe toxicity).

If pembrolizumab is discontinued, the participants may continue with cisplatin and radiation therapy.

Table 5 Dose Levels for Cisplatin

	Dose Level 0	**Dose Level -1**	**Dose Level -2**	**Dose Level -3**
Cisplatin	100 mg/m^2	80 mg/m^2	60 mg/m^2	Discontinue

7.2.3.1 Cisplatin-Related Toxicity

The major dose-limiting toxicities observed with single-agent cisplatin are the following:

- Gastrointestinal toxicity: nausea and vomiting.
- Nephrotoxicity: renal function impairment associated with tubular damage and manifested with elevation in serum creatinine and urea and decrease in CrCl. It is also associated with serum electrolyte disturbances, like hypomagnesemia, hypocalcemia, hyponatremia, hypokalemia and hypophosphatemia.
- Ototoxicity: cumulative and not reversible damage, manifesting with hearing loss in the high frequency.
- Hemotoxicity: neutropenia, thrombocytopenia, anemia.
- Neurotoxicity: manifesting with peripheral neuropathy and paresthesia in both upper and lower extremities.

7.2.3.2 Dose Modification for Cisplatin

For every treatment infusion, a full dose of cisplatin will be given if neutrophils are $\geq 1.0 \times 10^9$/L and platelets $\geq 75 \times 10^9$/L. If these levels are not reached, blood counts should be performed at the investigator's judgment but it is recommended at least weekly to document recovery. Once a participant has recovered, cisplatin should be administered (without waiting for the next cycle). If hematological toxicity has not resolved, the participant should not receive further cisplatin. The participant can continue with RT with or without pembrolizumab (depending on assigned treatment arm), and will be followed-up according to study protocol. Cisplatin may be administered up to 1 week following completion of RT.

The following dose reductions of cisplatin should be applied and should be carried over through all subsequent infusions (ie, no dose escalation). In the event that cisplatin treatment is stopped, no substitution with, for example, carboplatin, will be allowed. Cessation of cisplatin therapy is not, in itself, a reason for discontinuing the participant from the study.

<u>Dose Reduction for Neutropenia</u>

In the case of treatment delay due to delayed neutrophil recovery, the following policies are recommended:

- If neutrophil count has resolved to $\geq 1.0 \times 10^9$/L in ≤ 1 week, administer the full dose of cisplatin.
- If neutrophil count has resolved to $\geq 1.0 \times 10^9$/L in >1 week but ≤ 2 weeks, proceed with a dose reduction of cisplatin.

Dose Reductions for Febrile Neutropenia

In case of any febrile neutropenia (at least CTCAE 4.0 Grade 3: absolute neutrophil count <1000/mm^3 with a single temperature of >38.3ºC (101ºF) or a sustained temperature of ≥38ºC (100.4ºF) for more than 1 hour), it is recommended that the participant is hospitalized and treated with antibiotics as appropriate. After a period of febrile neutropenia, additional precautions have to be taken for the subsequent infusions and the cisplatin dose should be reduced.

Dose Reductions for Thrombocytopenia

If complicated thrombocytopenia ≥Grade 3, with hemorrhage and/or requiring prophylactic/therapeutic platelet transfusions (recommended at <10 × 10^9/L, but dependent upon local transfusion policy) occurs at any point during the treatment, appropriate supportive care should be given and cisplatin treatment should be delayed until platelets are ≥75 × 10^9/L.

In any case at the occurrence of Grade 4 thrombocytopenia at nadir (<25 × 10^9/L), cisplatin dose reduction should take place in the subsequent infusion.

Dose Reduction for Renal Toxicity

In case of renal toxicity, the cisplatin dose must be reduced as in Table 6:

Table 6 Cisplatin Dose Reduction for Renal Toxicity

Creatinine Clearance	**Cisplatin**
≥60 mL/min	100 mg/m^2
50-59 mL/min	80 mg/m^2
40-49 mL/min	60 mg/m^2
<40 mL/min	Discontinue

Dose Reduction for Peripheral Neuropathy

A neurological examination should be performed at screening, before the second cisplatin injection per local regulations by the investigator or qualified designee. In case of symptoms or signs experienced by the participant, more frequent examinations should be performed per local regulations by the investigator or qualified designee and the following dose modifications are required:

Grade 0, 1 (CTCAE v.4.0): No change.

Grade 2 (CTCAE v.4.0): Cisplatin will be reduced to 60 mg/m^2.

Grade ≥3 (CTCAE v.4.0): Cisplatin will be discontinued.

Dose Reduction for Ototoxicity

Cisplatin is known to cause high frequency hearing loss. Follow local product label and institutional guidelines (eg, for France see Appendix 7 for the most recent version of the medicines SmPC). The following dose modifications are required:

- If Grade 1 or 2 hearing loss (CTCAE v.4.0) occurs, the risk of additional hearing loss versus the potential benefit of continuing cisplatin chemotherapy should be made.
- Grade 3 and 4 hearing loss (CTCAE v.4.0) is an indication to discontinue cisplatin.

Dose Modification for Other Toxicities

If toxicity has not resolved the participant should not receive further cisplatin. The participant will continue with RT and will be followed-up according to the study protocol. Cisplatin can be administered up to 1 week following completion of RT.

Please also refer to the Multinational Association of Supportive Care in Cancer and European Society for Medical Oncology guidelines for treatment and prevention of emesis caused by highly emetic compounds [Roila, F., et al 2016]. Dose Modification for Cisplatin for other toxicities are presented in Table 7.

Table 7 Dose Modification for Cisplatin – Other Toxicities

Category	Toxicity	Hold Cisplatin Treatment for Grade	Timing for Restarting Cisplatin Treatment	Dose Level for Restarting Cisplatin Treatment	Discontinue Platinum
Non-hematologic	Creatinine clearance Decreased	Please see Table 6 for guidance on dose level reduction and discontinuation.			
	All other non-hematologic toxicities[b]	3-4[a]	Toxicity resolves to Grade 0-1	Reduce by 1 dose level	Toxicity does not resolve or if >2 Dose Level reductions exceeded
	Laboratory adverse event[b]	4	Toxicity resolves to Grade 2 or less	Reduce by 1 dose level	Toxicity does not resolve or if >2 Dose Level reductions exceeded

[a.] Permanent discontinuation should be considered for any severe or life-threatening event. Consult Sponsor before restarting treatment after Grade 4 drug-related AE

[b.] Participants with intolerable or persistent Grade 2 drug-related AEs may hold at physician discretion. Permanently discontinue from cisplatin for persistent Grade 2 adverse reactions for which treatment has been held, and did not recover to Grade 0-1 of the last dose. With investigator and Sponsor agreement, participants with a laboratory AE still at Grade 2 may continue in the study only if asymptomatic and controlled.

7.3 Method of Treatment Assignment

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 study treatment arms. Participants will be assigned randomly in a 1:1 ratio to pembrolizumab plus SoC (Arm A) and SoC (Arm B), respectively.

7.3.1 Stratification

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

- Primary tumor site (oropharynx/oral cavity vs. larynx vs. hypopharynx)
- Tumor Stage III vs. IVA
- PD-L1 status defined by TPS 50% (TPS≥50% vs. TPS<50%)

7.4 Blinding

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

Imaging and pathology data for the planned study analyses will be centrally reviewed by independent radiologist(s) and pathologist(s), respectively, without knowledge of participant treatment assignment. The participant-level PD-L1 biomarker results will be masked in the database to the investigator (see Section 10.2).

7.5 Preparation/Handling/Storage/Accountability

7.5.1 Dose Preparation

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

Preparation of cisplatin should follow the local product label (eg, for France see Appendix 7 for the most recent version of the medicines SmPC). The body surface area in m^2 should be calculated per local guidance.

7.5.2 Handling, Storage and Accountability

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

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

For all trial 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 trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

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

7.6 Treatment Compliance

The total volume of study medication infused will be compared with the total volume prepared to determine compliance with each dose administered.

Interruptions from the protocol specified treatment plan due to medical/surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, participant vacation, and/or holidays) >6 weeks between pembrolizumab doses and/or >12 weeks between pembrolizumab doses for drug-related AEs associated with pembrolizumab exposure (see Section 7.2.1 for dose modification guidelines for drug-related events) require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

7.7 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during study treatment through follow-up (refer to Appendix 8 for Germany-specific guidances). If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study therapy may be required. The investigator should discuss any questions regarding this with the Sponsor 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 treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

The following are prohibited concomitant therapy or vaccination during the course of the study:

1. Antineoplastic systemic chemotherapy or biological therapy, including prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).

2. Immunotherapy not specified in this protocol
3. Chemotherapy not specified in this protocol
4. Radiation therapy not specified in this protocol, including prior RT for the HNC under study.
5. Investigational agents other than pembrolizumab, including prior use of investigational agents for the HNC under the study.
6. Live vaccines within 30 days prior to the randomization, while participating in the study and receiving study treatment, and for 3 months after the end of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines, and are not allowed. Refer to Appendix 8 for Germany-specific requirements.

   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.
7. Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor. Note the following:

- A short course of steroids may be used as concomitant medication for either treatment of an AE or medical condition with Sponsor approval.
- Inhaled steroids are allowed for management of asthma.
- Use of prophylactic corticosteroids to avoid allergic reactions (eg, to IV contrast dye) is permitted.
- Use of steroids for antiemetic purposes is permitted.
- Use of steroids for premedication for study treatment is permitted.

8. No upfront prophylactic growth factor support with granulocyte-colony stimulating factor is allowed during CRT treatment. However, treatment of neutropenia with granulocyte-colony stimulating factor is allowed, if clinically indicated. Use of erythropoietin is not permitted.

9. During Cisplatin treatment only: Cisplatin is a potentially nephrotoxic drug which can be potentiated by other nephrotoxic agents such as aminoglycoside antibiotics. Use of aminoglycosides (such as streptomycin, dihydrostreptomycin, kanamycin, gentamicin, neomycin, tobramycin, netilmicin, and amikacin) should be administered with caution given the risk of nephrotoxicity. The serum creatinine, blood urea nitrogen, and electrolytes should be monitored carefully when additional nephrotoxic agents are used. Participants receiving cisplatin and other potentially ototoxic drugs such as aminoglycosides should also be closely monitored for signs of ototoxicity. If the administration of aminoglycosides is required, additional audiometric testing may be necessary for further safety monitoring. Please contact the Sponsor if aminoglycosides are administered to a study participant in order to discuss renal management as well as frequency of audiometric assessments. Refer to Appendix 8 for Germany-specific guidance.

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

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

All concomitant medications received within 28 days prior to randomization and up to 30 days after the last dose of study treatment should be recorded. Concomitant medications administered 30 days after the last dose of study treatment should be recorded for SAEs and ECIs as defined in Section 9.3.

There are no prohibited therapies in the Post-Treatment Follow-up Visits.

7.7.1 Rescue Medications & Supportive Care

7.7.1.1 Supportive Care Guidelines for Pembrolizumab

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined in Section 7.2 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.

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance.

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

7.7.1.2 Supportive Care Guidelines for Surgery

Supportive care will be provided as per local SoC and any AEs will be captured in the database (see Section 9.1.10.2.3).

7.7.1.3 Supportive Care Guidelines for Radiation

Supportive care will be provided as per local SoC (see Section 9.1.10.1.2.3)

7.7.1.4 Supportive Care Guidelines for Cisplatin

See Section 9.1.10.1.3

7.8 Treatment After the End of the Study

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

7.9 Clinical Supplies Disclosure

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

8 DISCONTINUATION/WITHDRAWAL CRITERIA

8.1 Discontinuation of Study Treatment

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

As certain data on clinical events beyond study treatment 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 treatment. Therefore, all participants who discontinue study treatment prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 2 - Schedule of Activities and Section 9.1.11 – Withdrawal/Discontinuation.

Participants may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study treatment by the investigator or the Sponsor if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 9.1.11 – Withdrawal/Discontinuation.

A participant must be discontinued from study treatment 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 treatment.
- 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 treatment.
- The participant has a confirmed positive serum pregnancy test.
- BICR verified radiographic disease progression outlined in Section 9.2.1.4.
  - Exceptions:
    - Participants with no histologic evidence of invasive cancer after definitive biopsy of the progressed lesion will not meet criteria for an event.
  - Radiographic disease progression during the neoadjuvant phase that precludes surgery will be considered an event.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.
- Recurrent Grade 2 pneumonitis.
- Completion of 17 doses of treatments with pembrolizumab.

  Note: 2 doses of study medication (pembrolizumab) are administered prior to surgery, at 3-week intervals from the date of the first dose. A subsequent 15 doses are administered post-surgery, calculated in 3-week intervals from the date of the first dose post-surgery.
- Administrative reasons.

Refer to Appendix 8 for additional Germany-specific guidance.

For participants who are discontinued from study treatment but continue to be monitored in the trial, all visits and procedures, as outlined in the SoA, should be completed.

Discontinuation from study treatment is "permanent." Once a participant is discontinued, he/she shall not be allowed to restart study treatment.

8.2 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 treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from Future Biomedical Research, are outlined in Section 9.1.11 – Withdrawal/Discontinuation. Refer to Appendix 8 for additional

Germany-specific guidance. 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 8.3.

8.3 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, phone 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 amount of missing data for the participant will be managed via the pre-specified data handling and analysis guidelines.

9 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 assuring that procedures are conducted by appropriately qualified or trained staff. Delegation of trial site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before providing documented informed consent may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. 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, including any extra assessments that may be required are detailed in the Vendor Manual.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Refer to Appendix 8 for country-specific requirements.

9.1 Administrative and General Procedures

9.1.1 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 or Future Biomedical Research. 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.

9.1.1.1 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.

9.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the Future Biomedical Research consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to Future Biomedical Research. A copy of the informed consent will be given to the participant before performing any procedure related to Future Biomedical Research.

9.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the study.

9.1.3 Participant Identification Card

All participants will be given a Participant Identification Card identifying them as participants in a research study. The card will contain trial site contact information (including direct telephone numbers) to be utilized 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 treatment allocation/randomization, site personnel will add the treatment/randomization number to the Participant Identification Card.

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

9.1.4 Medical History

Demographics and a complete medical history, including details of alcohol and tobacco, usage 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 significant. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

9.1.4.1 Disease Details

Details regarding participants HNSCC status at baseline must be thoroughly evaluated by the investigator or qualified designee and recorded in the appropriate eCRF including: date of initial diagnosis, stage at diagnosis, tumor grade, primary tumor location and type (ie, single lesion, multifocal), tumor, node and metastasis staging at baseline, etc. Refer to Sections 6.1 and 6.2 to ensure participant's disease status meets the relevant inclusion and exclusion criteria for study entry.

9.1.5 Prior and Concomitant Medications Review

9.1.5.1 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 prior to randomization. Prior treatment for other cancers will also be recorded as a prior medication.

9.1.5.2 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. All medications related to reportable AEs, SAEs and ECIs, including AEs and SAEs following definitive surgery should be recorded as defined in Appendix 4.

9.1.5.3 Post-study Anticancer Therapy Status

Investigator or qualified designee will record anticancer therapy medication, if any, taken by the participant after discontinuing from study treatment and through study follow-up.

9.1.6 Presurgery Tumor Tissue Collection

In accordance with the study inclusion criteria, participants are required to provide baseline tumor tissue from FFPE tissue specimens, obtained during the participant's initial diagnosis, for PD-L1 and HPV assessment.

HPV p16 testing

Participants must have assessment of HPV status from tumor tissue prior to randomization (see Section 6.1). In this study, HPV testing may be performed using local testing of HPV p16 status in participants with oropharynx cancer using the specified method. Oral cavity, hypopharynx, and larynx cancer are not required to undergo local HPV testing as by convention these tumor locations are assumed to be HPV-negative.

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

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

A tissue sample (regardless of tumor location: oropharyngeal, oral cavity, hypopharynx, or larynx cancer) used for PD-L1 testing can be used for HPV testing if required (see Vendor Manual).

PD-L1 testing

Participants must have central laboratory assessment of PD-L1 status from tumor tissue prior to randomization for stratification (see Section 6.1).

This specimen may be the diagnostic sample for participants with a new diagnosis of LA HNSCC.

9.1.7 Survival Status

All participants that are on study will receive on study follow-up as specified in the Section 2 – Schedule of Activities until Year 5 and thereafter every 3 months (91 ±14 days) to assess for survival status until death, withdrawal of consent, or at the end of the study, whichever occurs first. Once a participant experiences an event/disease progression/recurrence verified by BICR review, the participant should still be assessed for survival status every 3 months (91 ±14 days). Survival status could be collected by telephone contact. When assessing for survival status for participants in survival follow-up who have not experienced an event/progression, also evaluate and document whether the participant has had additional imaging assessments or biopsy-confirmed progression (see Section 2.4).

To ensure current and complete survival data is available at the time of database locks, the Sponsor may request survival status to be assessed at additional time points during the course of the study. For example, these additional assessments may be requested prior to an eDMC safety review, IA, and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a previously recorded death event in the collection tool).

9.1.8 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization. Each participant will be assigned only one screening number. Screening numbers must not be re-used for different participants.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 9.10.1.

9.1.9 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.

9.1.10 Treatment Administration

Study medication will be administered by the investigator and/or study staff according to the specifications within the Pharmacy Manual.

For the pembrolizumab arm (Arm A), presurgery neoadjuvant treatment (Treatment 1) should begin within 3 days of randomization. The timeframe for surgery (after the presurgery visit) is within 6 weeks (±10 days) after randomization. Participants in Arm A are allowed to go to surgery outside of this timeframe if delays are due to an AE. Participants with delays other than for an AE may be considered with sponsor consultation. In the SoC arm (Arm B), following randomization participants will proceed directly to surgery as per local practice. In both treatment arms, post-surgery adjuvant treatment will start when participants have recovered adequately from the morbidity and/or complications from the surgery with RT ± cisplatin starting at a recommended minimum range of within 6 weeks after surgery.

9.1.10.1 Timing of Dose Administration

The dose and schedule modifications of pembrolizumab, cisplatin and RT are provided in Section 7.2 - Dose Modification (Escalation/Titration/Other).

9.1.10.1.1 Pembrolizumab (Arm A Only)

Pembrolizumab will be administered on Day 1 of each 3-week dosing cycle after all procedures and assessments are completed according to the SoA (Section 2.0).

Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. 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 between -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes-5 min / +10 min).

Participants in Arm A are to receive 2 cycles of pembrolizumab presurgery in the neoadjuvant treatment phase. Each cycle is 21 days. Note: Participants in the pembrolizumab arm (Arm A) may proceed to surgery after 1 dose of pembrolizumab, if deemed appropriate, if the investigator has documented clinical evidence of tumor progression, preferably supported by radiographic evidence.

Participants in Arm A can start to receive pembrolizumab as adjuvant, once they have recovered adequately from the morbidity and/or complications from the surgery, as determined by the investigator. Post-surgery, participants can receive up to 4 doses of pembrolizumab Q3W, prior to the start of RT ± cisplatin, and if RT ± cisplatin is delayed the timing of these doses can be adjusted based on timing of surgery. If this occurs, assessments obtained for cycles of pembrolizumab administered prior to initiation of RT should mimic assessments required on cycle 2 day 1 of adjuvant treatment for Arm A in the SoA, except ePROs should only be obtained during RT, as outlined in the SoA. The weekly visits outlined in cycles 1 and 2 of the SoA should be completed during RT as weekly visits are only required during RT.

In addition, participants can receive pembrolizumab during RT ± cisplatin and then continued as monotherapy for a total number of 15 pembrolizumab infusions post-surgery (total duration of pembrolizumab ~1 year). If, within 3 weeks of surgery, pembrolizumab was not started because participants have not recovered adequately, pembrolizumab will restart concurrently with RT ± cisplatin.

For the combination portions of the study, treatment will be administered in the order: Pembrolizumab infusion is administered first followed by cisplatin infusion (high-risk participants only) and then RT.

Participants may receive up to 17 cycles of pembrolizumab in total. If an interruption occurs, the participant should restart pembrolizumab as soon as medically appropriate with the subsequent cycle, and should not skip cycles. The participant, after an interruption, may restart pembrolizumab cycles without delay from the original 3-week interval schedule, but all future doses should be recalculated in 3-week intervals. Participants should be administered all planned 17 cycles, which could extend beyond the 1-year timeframe of the study. If a dose of pembrolizumab is skipped and additional treatment cycles are required to reach 17 doses of pembrolizumab, perform all assessments in the additional cycles as indicated in the SoA (Section 2.2) under Cycle 8-15.

The Pharmacy Manual contains specific instructions for the pharmacist for the preparation of the pembrolizumab infusions and administration of infusion solutions.

9.1.10.1.2 Radiotherapy

It is recommended that RT is started within 6 weeks after surgery. All participants in the study will be treated with 6 to 10 MV photons. The administration of standard fractionated RT regimen should follow the dose parameters in Table 8. Linear accelerator or Tomotherapy based equipment is allowed. Use of intensity modulated radiation therapy (IMRT) is required, with either a sequential boost technique or Simultaneous Integrated Boost (SIB-IMRT).

Center credentialing will be performed according to criteria defined in the RT QA Manual. Participating institutions must comply with the RT QA requirements and procedures described in the RT QA manual. Sites that do not conform to the requirements of the credentialing will not be allowed to participate.

Both static and dynamic techniques IMRT techniques (including VMAT) are allowed. Dose planning, prescription, specification and reporting will be done according to International Commission on Radiation Units (ICRU) report 83 recommendations. Dose-volume constraints will be used for both dose specification and dose reporting in planning target volume (PTV) and planning organs at risk volumes (PRV)/organs at risk (OAR) (see Section 9.1.10.1.2.1). The dose-volume objectives that will be used for planning, dose specification and dose reporting in PTV, PRV and OAR are described in Section 9.1.10.1.2.1.

Table 8 Radiotherapy Dose Parameters

	Sequential Boost Plan	**Simultaneous Integrated Boost (followed by additional boost if needed)**
Low Risk for Microscopic Disease[a]	50 - 54 Gy in 25 - 27 fractions	54 Gy in 30 fractions
Intermediate Risk for Microscopic Disease[b]	60 Gy in 30 fractions	60 Gy in 30 fractions
Regions at High Risk[c]	66 Gy in 33 fractions	66 Gy in 33 fractions
Gross Residual Tumor[d]	70 Gy in 35 fractions	70 Gy in 35 fractions

CTV=clinical target volume; GTV=gross tumor volume; IGRT=image guided radiation therapy; PTV=planning target volume; RT=radiotherapy.

a. CTV_5000 or CTV_5400 defined as the area that is low risk for microscopic disease. This is the non-dissected neck. This RT dose is applicable for participants in the low-risk and high-risk groups.

b. CTV_6000 defined to include the post-operative tumor bed and nodal regions at risk of microscopic spread that have not been operated on according to standard anatomic guidelines relative to location and extent of gross disease. Please note all operated sites should receive 60 Gy. This RT dose is applicable for participants in the low-risk and high-risk groups.

c. CTV_6600 defined to include 0.5 cm expansion on regions thought to be at high risk of recurrence (eg, areas of extranodal extension or positive margins of resection). This RT dose is applicable for participants in the high-risk group.

d. For participants who do not undergo planned curative surgery or for incomplete resection with gross residual tumor: primary surgical tumor bed encompassing preoperative GTVs plus up to 0.5 cm to define CTV_7000.

All PTVs defined as 0.3 to 0.5 cm expansions on CTVs based on method and frequency of IGRT.

Radiotherapy treatment for participants that undergo surgery will be delivered over 6 to 6.5 weeks, depending on risk of recurrence, by incorporating 5 fractions per week (example: 5 fractions over 5 days (1 fraction per day), 2 days off).

Participants that do not undergo surgery as planned, for whatever reason, and proceed directly to salvage CRT may receive a RT dose of 70 Gy (total of 35 fractions) over 6.5 to 7 weeks.

When Sequential Boost IMRT is used, planning and delivery should be as follows: 50 Gy in 25 fractions or 54 Gy delivered in 27 fractions of 2 Gy/fraction, followed by a boost of 6 Gy in 3 additional fractions of 2 Gy/fraction. If an additional boost is required for high risk area such as areas of extranodal extension and/or positive margins, an additional 6 Gy can be delivered in 2 Gy/fraction in 3 fractions.

If SIB-IMRT is used, potential planning and delivery can be as follows: 60 Gy delivered in 30 fractions of 2 Gy/fraction given simultaneously with 54 Gy in 1.8 Gy/fraction. If an additional boost is required for high risk area such as areas of extranodal extension and/or positive margins, an additional 6 Gy can be delivered in 2 Gy/fraction for 3 fractions.

If all of the surgical area is considered at high risk for disease recurrence, another potential prescription option can be 66 Gy fractions given in 33 fractions at 2 Gy/fraction.

If gross disease is identified, in the case of a participant with incomplete resection, an additional boost up to 70 Gy may be delivered to the gross disease area.

If there is any doubt of the level of risk for recurrence after surgery but before RT based on physical examination and/or imaging, pathologic confirmation prior to start of RT is highly encouraged.

For participants in Arm A receiving treatment with pembrolizumab, the radiotherapy plan should be based on disease evaluation completed prior to initiation of neoadjuvant treatment regardless of response to treatment. An exception to this is that, in cases of tumor progression, a more extensive radiotherapy plan could be necessary for adequate coverage of tumor.

Questions relating to target volume delineation, treatment planning and treatment delivery can be submitted to the Sponsor as detailed in the RT QA Manual.

Radiotherapy plans for each participant should be submitted for approval to the RT vendor with any additional documentation as detailed in the RT QA Manual prior to initiation of RT.

Participant position and data acquisition

All participants will be irradiated in the supine position. Immobilization devices such as customized masks have to be used to ensure the accuracy and reproducibility of participants positioning during RT. Preferably, mask immobilization of the head, neck and shoulders will be used. For all participants, a planning CT scan will be performed in the immobilization device to capture slices extending from the level of the base of skull to the lower border of the clavicle. Slice thickness of preferably 2 to 3 mm will be used. Images will be constructed with at least 512 × 512 pixel matrices. It is acceptable to have the simulation CT scan as part of the diagnostic PET/CT scan with IV contrast so long the slice thickness is ≤3 mm.

To enhance vascular and soft tissue contrast and to facilitate delineation of both target volumes and OAR's the use of IV contrast enhancement is strongly recommended during simulation, unless medically contraindicated. If IV contrast is not used for the planning scan, it is mandatory the participant has either a contrast enhanced diagnostic CT and/or MRI performed no longer than 4 weeks prior to simulation. A PET/CT scan is encouraged to obtain a baseline status after surgery but before post-operative RT. This scan should be performed at least 4 weeks after surgery to minimize inflammation secondary to surgery. These images will have to be co-registered to the planning CT for contouring purposes and will be submitted along with the planning CT for QA.

9.1.10.1.2.1 Volume Definition

The definition of volumes will be in accordance with ICRU Reports #50, #62 and #83 [ICRU 1993; ICRU 1999; ICRU 2010]. Volumes will be named according to the target and OAR naming convention published by Santanam et al (2012) [Santanam, L., et al 2012].

Gross Tumor Volume (GTV)

A GTV will be defined only in cases where surgery was not performed or there is a concern of gross tumor identified post-operatively and where further surgery is not possible. In those cases a primary GTV (labeled GTVp) will be defined as all known areas of gross disease determined from CT, MRI, clinical information, and endoscopic findings. A nodal GTV (labeled GTVn) will encompass grossly involved lymph nodes defined as those >1.5 cm in long axis or >1 cm in short (axial) axis or nodes of any size with radiologic evidence of necrosis. Acceptable diagnostic imaging studies will include contrast enhanced CT and MRI and may be co-registered with the planning CT data set to facilitate GTV delineation. Fluorodeoxyglucose-positron emission tomography if available may be used to guide tumor identification but should not be used to define GTV borders given the uncertain relationship between the margin of the PET signal and tumor border.

Clinical Target Volumes

Clinical target volumes (CTVs) will be defined and named according to the doses intended to be delivered. The CTV_6000 will encompass the post-operative bed along with any areas considered at risk of microscopic tumor involvement (including nodal levels at risk). The CTV_6600 will encompass the highest risk disease area (ie, areas of extranodal extension and/or microscopic positive margin). The CTV_6600 is encompassed within CTV_6000. The CTV_5000 or CTV_5400 will encompass the lower risk microscopic region, typically the non-surgically violated area.

Clinical Target Volumes are defined as described below, limited according to natural barriers of spread and expanded to include anatomic regions at risk of microscopic spread. A high risk volume may be defined at the clinical discretion of the treating physician with defined individual department protocols. This optional volume can be used when the investigator prefers to give a higher dose than the microscopic risk region understanding it does not harbor gross tumor. Often, this volume encompasses areas of extranodal extension and/or positive margins.

Please note that the oral cavity composes of lip, buccal mucosa, oral tongue, floor of mouth, gingiva, hard palate, and retromolar trigone. Each of these subsites within the oral cavity have different patterns of spread which needs to be encompassed within the respective CTVs. A more detailed description of coverage of each of these subsites is provided in the RT QA Manual.

Clinical Target Volume for Gross Residual Disease (CTV_7000)

The CTV_7000 will consist of a 5 mm isotropic expansion of the GTVp and a 5 mm isotropic expansion of the GTVn. The CTV_7000 should be constrained to exclude regions protected by physical or anatomic barriers such as air (cavities or external to participant contour), bone (mandible or vertebral body) or fascial planes through which tumor spread is not apparent.

The CTV_7000 will be contained within the CTV_6000 and CTV_5000 or CTV_5400 defined to cover microscopic disease/prophylactic nodal regions at risk.

Clinical Target Volumes for Regions at High Risk of Tumor Recurrence (CTV_6600)

The CTV_6600 will encompass the post-operative tumor bed along with any areas considered at risk of microscopic tumor involvement. This volume will be used when the investigator prefers to give a higher dose than the microscopic risk region understanding it does not harbor gross tumor. It will be defined at the clinical discretion of the treating physician based on the pathology report after surgical resection.

Clinical Target Volumes for Regions at Low or Intermediate Risk of Microscopic Tumor Involvement

The CTV_6000 and CTV_5000 or CTV_5400 will encompass:

1. A 5 to 10 mm expansion on the post-operative tumor bed constrained to exclude regions protected by physical or anatomic barriers such as air (cavities or external to participant contour), bone (mandible or vertebral body) or facial planes through which tumor spread is not apparent.
2. Nodal levels deemed at risk of microscopic tumor involvement. The neck node levels will be delineated on each CT slice according to the updated guidelines defined by a consensus panel for the node-negative and the node-positive neck [Gregoire, V., et al 2014]. In case of infiltration (or suspicion of infiltration) of the sternocleidomastoid muscle, the muscle will be included in the low to intermediate risk CTVs.

Delineation of the Planning Target Volume

Planning target volumes PTV_7000, PTV_6600, PTV_6000 and PTV_5000 or PTV_5400 will be defined to enclose the corresponding CTV, respectively. Radiation dose will be prescribed, planned, and evaluated to these PTVs. Planning Target Values are used to account for participant movement, variation and residual error in day to day setup and will be generated by an isotropic expansion of their associated CTVs. Centers employing image guided radiation therapy (IGRT) using daily volumetric imaging (accelerator mounted kV or MV cone beam or tomotherapy MV CT) may generate PTVs with a 3 mm expansion. All others must use a 5 mm expansion.

In cases for which disease extends close to the participant external contour, depending on the equipment used, tissue equivalent bolus may be used to properly irradiate all parts of the

CTV, and the PTV extended to the external contour beneath the bolus. Planning Target Values will also be limited in regions where they may overlap with critical organ PRVs (spinal cord and brains stem) see Table 9. In cases that do not have skin involvement with disease, the PTV does not have to extend beyond the skin surface.

Delineation of Organs at Risk

Standard OARs are included in the following list and must be contoured on the planning CT data set according to the guidelines of Brouwer et al [Brouwer, C. L., et al 2015], utilizing the indicated naming convention. Guidelines for OAR contouring are provided in Table 9 and as published by Brouwer et al [Brouwer, C. L., et al 2015].

Table 9 Standard Organs at Risk

OAR	Standard Name
Spinal cord	SpinalCord
Brain stem	BrainStem
Lips	Lips
Oral cavity (beyond PTV)	OralCavity
Mandible	Mandible
Right Parotid	Parotid_R
Left Parotid	Parotid_L
Right Submandibular	Submandibular_R
Left Submandibular	Submandibular_L
Pharynx (beyond PTV)	Pharynx
Cervical Esophagus (beyond PTV)	Esophagus
Optic structures if needed	Optic-Structures
Larynx	Larynx
Cochlea	Cochlea
External border of participant	External
Abbreviations: OAR = organs at risk; PTV = planning target volume	

Planning Organ at Risk Volume

A planning OAR volume (PRV) for the critical OARs spinal cord and brainstem will be generated with an isotropic expansion for the purpose of dose evaluation and limitation to these structures. The PRVs represent a safety margin for these critical structures to account for variability in day to day positioning. Centers utilizing daily volumetric imaging (accelerator mounted kV or MV cone beam or tomotherapy MV CT) may generate PRVs with a 3 mm expansion. All others must use a 5 mm expansion.

Treatment Planning

Participants will be treated by IMRT or volumetric modulated arc RT using 6 to 10 MV photons. For linear accelerators, field arrangements are left to the discretion of the medical physicists to produce an optimal dose distribution matching the dose-volume constraints for PTV, PRV and OAR. Non-coplanar field arrangements are allowed, but beam directions through the eyes are not allowed unless unavoidable. All field entrance and exits should be within the planning CT range in order to avoid any inadequate dose calculations.

Treatment plans will be computed using modern type B dose calculation algorithms such as convolution/superposition, Monte Carlo, collapsed cone or equivalent algorithms. The dose calculation matrix to be used must be less than 4 mm. Dose calculations must account for tissue heterogeneity.

The following dose-volume objectives (Table 10) will be used for planning, dose specification and dose reporting for PTV, PRV and OAR:

Table 10 Dose Volume Objectives

PTV		**Dnear-min**	**Dnear-max**		**Median Dose**	
OAR / PRV	**D95%[1]**	**Or D98 %**	**Or D2%**	**D5%**	**Or D50%**	**Mean Dose**
PTV_7000	≥95% of planned dose	≥90% of planned dose	-	≤107% of planned dose	70 Gy ± 2%	-
PTV_6600 (optional high risk volume)	≥95% of planned dose	≥90% of planned dose	-	≤107% of planned dose	66 Gy ± 2%	-
PTV_6000	≥95% of planned dose	≥90% of planned dose	-	≤107% of planned dose	60 Gy ± 2%	-
PTV_5000 or PTV_5400	≥95% of planned dose	≥90% of planned dose	-	-	54 Gy or 50 Gy ± 2%	-
PRV spinal cord	-	-	≤45 Gy	-	-	-
PRV brain stem	-	-	≤50 Gy	-	-	-
Contralateral parotid	-	-	-	-	-	≤25 Gy
Ipsilateral parotid	-	-	-	-	-	≤30 Gy
Oral cavity	-	-	-	-	-	≤30 Gy
Larynx	-	-	-	<55 Gy	-	≤44 Gy
Mandible	-	-	≤70 Gy	-	-	-

[1] D_v: Dose in v% of the volume
Abbreviations: OAR = organs at risk; PRV = Planning Organ at Risk Volume; PTV = planning target volume.

9.1.10.1.2.2 Treatment Verification and Accuracy

All participants must have routine imaging performed to verify treatment set up. The minimum imaging requirement is once weekly orthogonal KV images commencing on the first day of treatment and reviewed by the managing radiation oncologist. Centers are strongly encouraged to employ daily volumetric image guidance with either accelerator mounted KV or MV cone beam CT or tomotherapy CT images utilizing matching of bony anatomy. The margin for PTV can be reduced to 3 mm if daily IGRT is performed.

Table 11 details radiotherapy compliance criteria.

Table 11 Radiotherapy Compliance Criteria

	Per Protocol	**Variation Acceptable**	**Deviation Unacceptable**
Prescription Dose	Delivered daily or total dose to any PTV is within 5% of the protocol dose.	Delivered daily or total dose to any PTV differs from the protocol specified dose by 6-10%	Delivered daily or total dose to any PTV differs from the protocol specified dose by >10%
Dose Uniformity	Dose to 95% of any PTV is > 95% of prescribed dose.	Dose to 95% of any PTV <95% of the prescribed dose; >10% of the highest dose PTV >110% of prescribed dose	Dose to 95% of any PTV <90% of the prescribed dose; >10% of the highest dose PTV >120% of prescribed dose
Volume	Volumes follow protocol guidelines	PTV margins are less than the protocol specified margins or excessively large	CTV does not encompass areas at risk.
Organs at Risk			Dose to 2% of PRV spinal cord >50 Gy Dose to 2% of PRV brainstem >54 Gy
Interruptions		Uncompensated Interruptions more than 2 days for reasons other than toxicity	Uncompensated Interruptions more than 10 days for reasons other than toxicity
Abbreviations: CTV = clinical target volume; PRV = Planning Organ at Risk Volume; PTV = planning target volume.			

9.1.10.1.2.3 Supportive Care for Head and Neck Radiotherapy

Radiation-induced head and neck toxicity is well known and has been well described. It is expected to vary according to the total dose and the concomitant use of chemotherapy. Locoregional toxicity will be monitored during treatment using CTCAE v. 4.0 and will be reported in the database. Supportive care will be provided according to local SoC.

Reversible mucositis and pharyngitis is expected, and supportive care will be initiated (eg, pain medication, mouth wash, adaptation of the diet, use of a nasogastric or percutaneous endoscopic gastrostomy feeding tube). In very rare cases of severe Grade 4 mucositis (eg, bleeding); it may be necessary to interrupt RT for a few days. However, it is mandatory to limit the break to a strict minimum.

Various degrees of skin reaction (typically Grade 2, less frequently Grade 3) are expected in the treated area. Other expected acute reactions include fatigue, xerostomia, dysgeusia, ageusia and dysphagia.

Central nervous system events in terms of nausea and vomiting are expected. Late effects include some degree of xerostomia and occasionally persistent dysphagia.

Mandibular osteoradionecrosis may occur in less than 5% of the participants. Thorough dental evaluation and, if necessary, adequate care performed before the start of RT, will substantially decrease this risk.

9.1.10.1.2.4 Treatment Interruptions / Modifications

Treatment interruptions are to be avoided unless medically necessary. Any breaks in RT should be minimized. See Section 7.2.2 – Dose Modification for Radiotherapy.

9.1.10.1.3 Cisplatin

Three doses of cisplatin will be administered to those participants, in both treatment arms, considered at high-risk of recurrence based on the pathological features ie, positive margins (< 1 mm) or extranodal extension in the surgical specimen assessed by the local pathologist. If there are delays in cisplatin treatment, cisplatin may be administered up to 1 week following completion of RT. Participants that deviate from receiving planned cisplatin due to medical considerations may continue on the study after discussion with Sponsor and review of dose modification options (see Section 7.2.3). Three doses of cisplatin are permitted in those participants that do not undergo planned surgery and proceed directly to salvage CRT.

Cisplatin will be administered after all procedures and assessments are completed according to the Schedule of Activities in Section 2.0.

Cisplatin is given as a dose of 100 mg/m^2 using an infusion duration of 60 minutes (or infusion duration according to local practice).

Note: For body surface area over 2 m^2 the cisplatin dose will be capped at the one calculated for body surface area = 2 m^2.

Before and after administration of cisplatin, adequate hydration is required and can be given as normally used in each institution. It is advised that participants can be hospitalized for at least 24 hours to allow optimal hydration before and after drug injection, if required per local regulations; or cisplatin may be administered on an outpatient basis, if adequate hydration can be managed and if allowed per local regulations. If hydration is performed as a planned hospitalization, it would not meet that criterion for SAE.

Administration of Cisplatin

The administration of cisplatin can follow the standard local practice and/or international guidelines. However, it is highly recommended to follow the instructions as reported below.

It is recommended that cisplatin start on the first day of RT (±2 days). Follow local product label and institutional guidelines. Cisplatin can be administered up to 1 week following completion of RT regimen.

Before starting the treatment with cisplatin, the following criteria must be met:

- Neutrophils: $\geq 1.0 \times 10^9$/L
- Platelets: $\geq 75 \times 10^9$/L
- Creatinine clearance: ≥60 mL/min (Cockcroft-Gault formula). It is recommended that participants whose creatinine clearance is <60 mL/min on the scheduled day of cisplatin administration receive IV fluid hydration for 1 to 2 days followed by a repeat CrCL. The cisplatin can be dosed based on the follow up CrCl level (see Table 6).

Recommendations:

- Encourage the participant to drink 2 to 3 liters of water per day during the days preceding and following cisplatin infusion.
- Any pre-existing dehydration must be corrected before starting the hydration related to cisplatin administration.
- Assess the hydration status during physical examination.
- Antiemetic medications should include:
  - serotonin type 3 antagonist (eg, granisetron 1-3 mg IV or ondansetron 8-32 mg IV or palonosetron IV 0.25 mg IV; 30 minutes before cisplatin infusion),
  - aprepitant (eg, 125 mg orally [per os; po] 30 minutes before cisplatin infusion and 80 mg/day PO during the 2 following days, or 150 mg IV on Day 1),

- corticosteroids (eg, dexamethasone 20 mg [12 mg if given with aprepitant] 30 minutes before cisplatin infusion and dexamethasone 8 mg twice per day [8 mg once per day if given with aprepitant] po during the 3 following days). Another equivalent corticosteroid regimen is allowed according to local practice. The maximum dose of steroids for antiemetic treatment or prophylaxis is 20 mg/day [12 mg if given with aprepitant] dexamethasone or its steroid equivalent),
- any "as-needed" antiemetics according to each institutional guideline (metoclopramide, alizapride, additional steroids, etc.).

- Intravenous pre- and post-hydration per local guidelines. Following cisplatin infusion, an overnight additional hydration is also allowable, per local regulations.
- Cisplatin infusion: mannitol before cisplatin infusion is allowed according to local practice. Cisplatin should be prepared according to local practice and should be infused over 60 minutes.
- Urinary output: >100 mL/hour before starting cisplatin infusion and also after cisplatin infusion during at least 4-6 hours (400 mL/4 hours). If this level is not reached, furosemide (LASIX® [furosemide, Sanofi Aventis]) 20 mg IV should be given.
- Participants may be weighed before and after cisplatin infusion, if weight gain furosemide (LASIX®) could be given.
- Replace potassium and magnesium as needed.
- Check for presence of ototoxicity.

9.1.10.2 Surgery Guidelines

9.1.10.2.1 Pre-operative Assessment

Preoperative assessment should proceed as per institutional guidelines and participant's Charlson co-morbidity index, ASA-score, and nutritional status are recommended to be assessed. Also routine hematology and chemistry tests will be performed as detailed in Section 2.0 – Schedule of Activities. Preoperative imaging should be performed as described in Section 2.0 - Schedule of Activities and Section 9.2.1 - Tumor Imaging and Assessment of Disease. In case of procedures with potential long-term swallowing compromise the treating surgeon may obtain pulmonary function tests or a barium swallow as per local SoC. Surgeons are recommended to document the primary tumor and lymphadenectomy surgical plan at initial evaluation. This may include either photo documentation or appropriate drawings to identify the planned surgical margin of resection (in case of tumor response with intervention).

9.1.10.2.2 Surgical Procedure Guidelines

Routine general anesthesia according to institutional guidelines should be performed. Perioperative antibiotics and steroids are administered per institutional guidelines. Surgeons are encouraged to avoid the use of steroids where possible. Prohibited medications are detailed in Section 7.7 – Concomitant Therapy. Any permitted perioperative steroids should

be administered after all study related tissue and blood samples have been collected where possible.

Surgical procedures are tailored to the location of the tumor. The standard surgical procedures for this study are detailed in the Surgical Brochure. Importantly, surgical resection should be performed to margins identified at initial presentation as documented by the surgeon in Section 9.1.10.2.1. Also, the planned lymphadenectomy determined at initial presentation should be performed as documented by the surgeon in Section 9.1.10.2.1. In case of tumor progression, a more extensive procedure could be necessary in order to achieve negative resection margins. All study related biopsies should ideally be collected prior to resection being completed. The resection at each site should provide margins of at least 5 mm in the primary specimen, unless there are surgical contra-indications ie, proximity of great vessels. For the pembrolizumab treatment arm, the original surgical margins determined prior to initiation of pembrolizumab should be used to guide surgical resection. The choice of procedure as well as the choice of reconstruction, if deemed necessary, is at the discretion of the surgeon as per local SoC. The surgeon should describe in their operation report the extent of macroscopic disease with particular comparison to extent at initial presentation.

9.1.10.2.3 Post-operative Complications

Complications after major head and neck surgery encompass intraoperative and post-operative issues. Intraoperative issues may include hemostasis and tissue quality during dissections. Post-operative complications may be local and include bleeding, infection, or wound healing issues including pharyngeal fistulas, chylous fistulas, spinal accessory, hypoglossal and/or facial nerves, and other local, regional or free flap failure. These may contribute to increased length of inpatient hospital stay and time to initiation of post-operative RT ± cisplatin. In the absence of guidelines for the management of those, it will be to the discretion of the treating surgeon to manage these complications at the best of his/her knowledge as per local SoC.

9.1.10.2.3.1 Evaluation and Reporting of Post-operative Complications

Surgical complications will depend on the extent of the procedures, the site of intervention, and the technique of reconstruction. Given the variety of possible interventions a large variety of complications have to be foreseen. Potential post-operative complications include, but are not limited to:

Endoscopy:

- Dysphagia
- Odynophagia
- Voice changes and hoarseness
- Dyspnea
- Teeth damage

- Esophageal perforation
- Mediastinitis

Tumor Resection with or Without Reconstruction (Free or Regional/local Flap):	
• Hemorrhage/hematoma (requiring drainage, blood transfusion, or surgical intervention to stop bleeding)	• Loss of voice and hoarseness
• Epistaxis	• Partial or total flap loss
• G-tube complication	• Seroma
• Infection (including flap donor site and tracheostomy site)	• Spinal accessory nerve damage
• Fistula	• Hypoglossal nerve damage
• Wound healing complication	• Vagal nerve damage
• Dysphagia	• Facial nerve damage
• Odynophagia	• Phrenic nerve damage
• Tracheostomy complication	• Sympathetic trunk damage (Horner syndrome)
• Trismus	• Chyle leak

All post-operative complications will be reported and graded in the same way as other AEs (see Appendix 4) and will be identified by the investigator and/or surgeon as post-surgical complications. See Section 9.3.1 for reporting requirements for all AEs and SAEs considered to be post-surgical complications by the investigator.

9.1.10.2.4 Post-operative Care

Post-operative rehabilitation should proceed per institutional guidelines. These relate to tracheostomy status and resumption of oral diet. In general, all efforts should be made to de-cannulate participants with tracheostomies as fast as possible and start the participant on an oral diet. Sites are encouraged to get early involvement from speech and language pathologists, as per institutional guidelines, and to mobilize the participant as fast as his/her condition allows. These decisions need to be made by the treating head and neck surgeon and should be individualized to the participant's ability and needs.

9.1.10.2.5 Pathology Specimen

The resection specimen submitted to a local pathologist should include an entire surgically resected lesion with appropriate orientation and all resected lymph nodes (as well as tumor bed, if applicable), as per the guidelines provided in the Surgical Brochure and Pathology Manual. On pathologic exam, margins are defined as negative if ≥5 mm from the invasive front of tumor, close margin if between 1-5 mm, and positive margin if <1 mm in the primary

resection specimen; an extranodal extension is defined as any extension of SCC from within a lymph node through the fibrous capsule and into the surrounding connective tissue. Surgeons may use margins from the tumor bed after resection and guidelines from the Surgical Brochure should be followed in this regard.

Neck dissection specimens should be processed per guidelines in the Vendor Manual but should include separation of the specimen into distinct neck levels prior to pathology submission.

Communication from surgeon to local pathologist should follow local practice and institutional guidelines. Sample transport, storage and shipment instructions for pathology specimens obtained during surgery will be provided in the Vendor Manual.

Representative specimens (slides) of tumor tissue collected during surgery from all participants will be submitted to the designated central laboratories (see Pathology Manual) for blinded pathological response assessment of the pCR and mPR endpoints, determination of high risk pathologic features (defined by evidence of positive margins or extranodal extension following surgical resection), and translational research (see Section 9.2.2).

9.1.11 Withdrawal/Discontinuation

Participants who discontinue study treatment prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits.

When a participant withdraws from participation in the study, all applicable activities scheduled for the End of Study Visit should be performed at the time of withdrawal. Any AEs which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 9.3 - Adverse Events, Serious Adverse Events and Other Reportable Safety Events.

Refer to Appendix 8 for Germany-specific guidance.

9.1.11.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for Future Biomedical Research. Participants may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@msd.com). Subsequently, the participant's consent for Future Biomedical Research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the

participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

9.1.12 Participant Blinding/Unblinding

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

9.1.13 Domiciling

Participants will be hospitalized for the protocol specified surgery and discharged as per local SoC.

At the discretion of the investigator, participants may report to the clinical research unit the evening prior to the schedule day of cisplatin administration and remain in the unit until 24 hours post-dose to ensure proper hydration. At the discretion of the investigator, participants may be requested to remain in the clinical research unit longer.

9.1.14 Calibration of Equipment

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

9.2 Efficacy Assessments

9.2.1 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the central imaging vendor can be found in the SIM. Tumor imaging (head and neck, chest, and upper abdomen) is strongly preferred to be acquired by CT with contrast. Magnetic resonance imaging of the head and neck and upper abdomen should be used when CT with iodinated contrast is contraindicated or when mandated by local practice, or for imaging of the brain. The upper abdomen CT/MRI should cover the liver in its entirety. The choice between CT and MRI for the head and neck and upper abdomen imaging is left to the discretion of the investigator, but the same imaging technique, regarding modality and the use of contrast should be used in a participant throughout the study to optimize the visualization of existing and new tumor burden.

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

When the investigator identifies radiographic progression per RECIST 1.1, the central imaging vendor will perform expedited verification of radiologic progressive disease (PD) and communicate the results to the study site and Sponsor via email (see Section 9.2.1.4). Treatment should continue until PD/recurrence has been verified, initiation of a new anticancer treatment, pregnancy, death, withdrawal of consent, study conclusion or early termination, whichever occurs first (refer to Sec 8.1 – Discontinuation of Study Treatment).

9.2.1.1 Initial Tumor Imaging

Initial tumor imaging at Screening (contrast enhanced head and neck, chest, and upper abdomen CT scan or chest CT scan plus head and neck and abdomen MRI, and FDG-PET or FDG-PET/CT) must be performed within 28 days prior to the date of randomization. The site study team must review screening images to confirm the participant has evaluable disease per RECIST 1.1 prior to submitting to central imaging vendor.

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

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

Fluorodeoxyglucose-positron emission tomography (FDG-PET or FDG-PET/CT) scans will only be performed at screening to help guide potential SoC neck dissections, if required. Diagnostic quality CT can be acquired on the PET/CT scanner while performing FDG-PET if that is the local standard practice (see procedure detail described in the SIM).

9.2.1.2 Tumor Imaging During the Study

The same modality (CT/MRI head and neck, chest, and upper abdomen) used at screening should be used during neoadjuvant and adjuvant treatment and during the post-treatment follow-up visits at the scheduled time points detailed in Section 2.0 – Schedule of Activities.

For participants in the pembrolizumab arm (Arm A), the first on-study imaging assessment should be performed after completion of 2 cycles of pembrolizumab treatment, at approximately Week 6 (±10 days) from the date of randomization and before surgery. If the presurgery scan shows tumor flare this should not alter the timing or decision to proceed to surgery unless the tumor is unresectable. In the SoC arm (Arm B), the screening imaging will serve as the presurgery imaging. If the presurgery scans for Arm A or baseline scans for Arm B are done > 14 days prior to the date of surgery, then repeat imaging prior to surgery will be required.

The first post-surgery imaging should be performed 12 weeks (± 7 days) after the end of RT ± cisplatin. Subsequent tumor imaging should then be performed every 3 months (91 ± 7 days), or more frequently if clinically indicated, until the end of Year 3 after randomization, then every 6 months (182 ±14 days) until the end of Year 5. For all post-surgery imaging, the clock will start at the end of RT ± cisplatin (ie, last dose of). All of these visits should stay on track using the last dose of RT ± cisplatin as the starting clock, ie,

if one of the imaging visits is late (even the first scan post-surgery), the participants will stay on the original schedule starting with the last dose of RT ± cisplatin for all future visits; do not recalculate. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. When the investigator identifies radiographic progression per RECIST 1.1, the site should submit the imaging with verification of progression (VOP) request to the central imaging vendor as soon as possible. Expedited VOP read will be performed by BICR and the results will be communicated to the site and Sponsor via email. If initial site-assessed PD was not verified by BICR, each subsequent imaging must be submitted to central imaging vendor with VOP request until PD has been verified. Treatment should continue until PD has been verified by BICR, initiation of a new anticancer treatment, pregnancy, death, withdrawal of consent, study conclusion or early termination, whichever occurs first. Of note, a participant will only discontinue from study treatment during the neoadjuvant phase if PD precludes surgery (refer to Sec 8.1 – Discontinuation of Study Treatment).

9.2.1.3 End of Treatment and Follow-up Tumor Imaging

For participants who discontinue study treatment without a documented event/disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every 3 months [91 ± 7 days] until the end of Year 3, thereafter every 6 months [182 ± 14 days] until the end of Year 5) to monitor disease status until an event/disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first. For participants who discontinue study treatment due to an event/documented disease progression, this is the final required tumor imaging.

9.2.1.4 RECIST 1.1 Assessment of Disease

During the neoadjuvant period and for those participants who do not have surgery RECIST 1.1 by BICR will be used as the primary measure for assessment of disease progression, locoregional failure status, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study therapy). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden. Initial tumor imaging showing site-assessed PD/recurrence should be submitted immediately to BICR for verification of PD/recurrence. The site will be notified if the BICR verifies PD using RECIST 1.1.

In the post-surgery adjuvant phase, imaging will be performed with assessments based on disease recurrence. If indicated, biopsy confirmation of recurrent lesion/s will be performed.

If an unplanned imaging is performed before 12 weeks after the end of RT ± cisplatin and disease progression is assessed per RECIST 1.1 and verified by BICR, this will be an EFS event.

The complete RECIST 1.1 criteria are included in the published RECIST document (available at http://www.eortc.be/RECIST).

9.2.2 Tumor Tissue Collection and Assessment of Pathological Response

All participants will undergo potentially curative surgical resection performed as part of the local SoC (see Section 9.1.10.2). Details regarding date of surgery, type of surgery, tumor resectability etc. will be recorded in the appropriate eCRF.

Detailed evaluation of tumor staging per AJCC Cancer Staging Manual (8th edition) and assessment of surgical margins will be performed by the local pathologist on all tissues removed during the surgery and recorded in the appropriate eCRF. Local pathology results will be used to guide post-surgery treatment decisions.

The primary evaluation of pathologic response (pCR or mPR) and assessment of surgical margins will be conducted by blinded central pathologists. In all cases, the central pathologist interpreting surgical specimens for assessment of pCR/mPR will be blinded to treatment assignment. A summary note will be provided to the study pathologist that includes a general overview of the study. The note should also include the major clinical, radiographic, and operative findings including a description or diagram of the original size and location of the tumor, the presence or absence of multifocality, the extent of preoperative lymph node involvement, and type of surgery. The study pathologists will send the representative specimens (slides) including surgical margin, the deepest focus of visible malignant epithelium in the head and neck, and any carcinoma found or suspicious cells in the lymph node for central pathologist confirmation, as detailed in the Pathology Manual.

All study pathologists will be required to complete formal training. The Pathology Manual will be provided, outlining standard guidelines for pathological evaluation of specimens.

For participants who do not achieve a pCR, a tumor tissue sample is to be collected and submitted to the designated central laboratory for translational research as specified in Section 5.4.1.4 – Planned Exploratory Biomarker Research. Any leftover tissue at the time of this surgery or any further head and neck surgeries will be archived for FBR if the participant has provided documented informed consent for FBR as specified in Section 5.4.1.5 – Future Biomedical Research.

An optional core biopsy may be collected post-surgery at the time of recurrence, if applicable, and submitted to the central laboratory for translational research, for participants who agree to participate, as specified in Section 5.4.1.5 – Planned Exploratory Biomarker Research. Any leftover tissue will be archived for FBR if the participant has provided documented informed consent for FBR as specified in Section 5.4.1.6 – Future Biomedical Research.

Detailed instructions for tissue collection, processing and shipment are provided in the Vendor Manual.

9.2.3 Survival

Event-free survival and OS data will be collected from the time of randomization throughout the study. Definitions of the survival endpoints are provided in Section 10.4.1 and censoring rules are presented in Section 10.6.1.

9.2.4 Patient Reported Outcomes

The EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ-H&N35 questionnaires will be administered by trained site personnel and completed electronically by participants in the following order: EQ-5D-5L first, then EORTC QLQ-C30, followed by EORTC QLQ-H&N35. The questionnaires are to be administered from baseline, defined as Treatment 1 Cycle 1 in the Pembrolizumab Arm (Arm A) or prior to surgery in the SoC Arm (Arm B), until Year 5 as specified in the Schedule of Activities (Section 2.0).

It is best practice and strongly recommended that electronic PROs (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.

9.3 Adverse Events, Serious Adverse Events and Other Reportable Safety Events

The definitions of an adverse event (AE) or serious adverse event (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 4.

AE, 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, who is a qualified physician, and any designees are responsible for detecting, assessing, 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 AE, SAEs and other reportable safety events for outcome according to Section 9.3.3.

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

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

AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before treatment allocation/randomization, must be reported by the investigator if the event causes the participant to be excluded from the trial, 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 treatment allocation/randomization through 30 days following cessation of study treatment must be reported by the investigator.
- All adverse events considered to be post-surgical complications by the investigator from time of protocol-specified surgery through 30 days following surgery, must be reported by the investigator.
- All AEs meeting serious criteria, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.
- All SAEs that are considered to be post-surgical complications by the investigator, from the time of protocol-specified surgery through 90 days following surgery or 30 days following protocol-specified surgery if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through the time required to eliminate systemic exposure after cessation of study treatment as described in Sections 6.1 and 9.5.9.2, or 30 days after cessation of study treatment 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 to be drug-related. Subjects in post-treatment follow-up will be actively followed for treatment-related late SAEs for up to 5 years.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment 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 timeframes as indicated in Table 12.

Table 12 Reporting Time Periods and Timeframes 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		Timeframe to Report Event and Follow-up Information to SPONSOR:
Non-Serious Adverse Event (NSAE)		Report if: - due to protocol-specified intervention - causes exclusion	Report all	Not required		Per data entry guidelines
Serious Adverse Event (SAE) including Cancer and Overdose		Report if: - due to protocol-specified intervention - causes exclusion	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)		Within 24 hours of learning of event
Pregnancy/ Lactation Exposure		Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome		Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)		Report if: - due to intervention - causes exclusion	Report - Potential 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

9.3.2 Method of Detecting AE, SAE and Other Reportable Safety Events

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

9.3.3 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 AE, SAE and other reportable safety events

including pregnancy and exposure during breastfeeding, ECI, 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 8.3). In addition, the investigator will make every attempt to follow all non-serious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 4.

9.3.4 Regulatory Reporting Requirements for SAE

- Prompt notification (within 24 hours) by the investigator to the sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment 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 treatment under clinical investigation. All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, ie, per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAE) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.3.5 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 9.3.1.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression/recurrence 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 which upon review is not progression of the cancer under study will be forwarded to global safety as a SAE within 24 hours of determination that the event is not progression of the cancer under study.

9.3.6 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered adverse events, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee), including the pregnancy of a male participant's female partner, that occurs during the trial are reportable to the Sponsor.

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

9.3.7 Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

Events of clinical interest for this trial include:

1. an overdose of study intervention, as defined in Section 9.4 – Treatment of Overdose, that is not associated with clinical symptoms or abnormal laboratory results.
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 trial site guidance for assessment and follow-up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

9.4 Treatment of Overdose

Pembrolizumab overdose

In this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater.

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

Cisplatin overdose

There is no specific antidote for cisplatin overdose. Overdose may result in the side effects associated with the drug occurring in an excessive manner.

Otherwise, overdose should be managed according to local label and practice.

Radiation Overdose

In this study, an overdose of radiation will be defined as any dose ≥20% over the prescribed dose for the CRT treatments. There is no specific antidote for radiation overdose. In the event

of an overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Reporting of overdose is detailed in Section 9.3 and Appendix 4.

9.5 Safety

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

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

9.5.1 Physical Examinations

A complete physical examination will be conducted as per institutional standard. Height and weight will also be measured and recorded.

A brief directed physical examination will be conducted as per institutional standard as per the Schedule of Activities (Section 2.0)

Investigators should pay special attention to symptom monitoring (eg, swallowing function) and clinical signs related to previous serious illnesses.

9.5.1.1 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam, including the presence/absence of feeding tube and a neurological exam (see Section 9.5.6), during the Screening period. Clinically significant abnormal findings should be recorded as medical history. Further full physical examinations will be performed prior to administration of RT ± cisplatin post-surgery (Treatment 2) and upon treatment discontinuation. The time points for full physical exams are described in Section 2.0. After the first dose of study treatment, new clinically significant abnormal findings should be recorded as AEs.

9.5.1.2 Directed Physical Exam

For cycles that do not require a full physical exam as defined in Section 2.0, the investigator or qualified designee will perform a directed physical exam, including the presence/absence of feeding tube and neurological exam, as clinically indicated prior to the administration of the study treatment. New clinically significant abnormal findings should be recorded as AEs.

9.5.2 Vital Signs, Height and Weight

The investigator or qualified designee will take weight and vital signs at screening and as specified in the Section 2.0 – Schedule of Activities; height will be measured at Screening only. Vital signs will be measured in a semi-supine position after 5 minutes rest and will

include temperature, systolic and diastolic blood pressure, pulse and respiratory rate. Vital signs should be measured prior to administration of each dose of study treatment and prior to blood collections.

9.5.3 Electrocardiograms

A standard 12-lead electrocardiogram (ECG) will be performed using local standard procedures once at screening. Clinically significant abnormal findings should be recorded as medical history. Additional time points may be performed as clinically necessary.

9.5.4 Performance Assessment

9.5.4.1 Eastern Cooperative Oncology Group Performance Status

The investigator or qualified designee will assess ECOG performance status (see http://ecog-acrin.org/resources/ecog-performance-status) at Screening, prior to dosing during each treatment cycle and during Post-Treatment Follow-up visits.

9.5.5 Oral and Dental Check-up

All participants should have an oral and dental examination including clinical and radiological examination by the investigator or other appropriate healthcare provider, per local institutional guidelines, during screening. When clinically indicated, extraction of dental elements should be carried out. The interval between extractions and start of RT ± cisplatin should be as long as possible to permit healing and participant comfort prior to the commencement of treatment. If more than 2 teeth are to be extracted this should be done prior to RT simulation. Oral/dental check-ups are recommended every 6 months throughout the study (can be per SoC/local guidelines). Adequate dental care (including daily fluorine application) should be recommended as an option to all participants, at least during follow-up. Documented routine oral and dental check-up performed within 6 weeks of randomization is acceptable and does not need to be repeated in Screening.

The frequency of oral and dental check-ups is as per local SoC, but it is recommended that participants have a check-up every 6 months during the study.

9.5.6 Neurological Examination

Neurological examinations will be conducted as part of the physical examinations and must be performed for all participants at Screening as per local standards by the investigator or qualified designee. For participants at high risk of recurrence post-surgery a neurological exam should be repeated before each cisplatin injection, and thereafter as clinically indicated. In case of symptoms or signs experienced by the participant, more frequent examinations should be performed per local standards by the investigator or qualified designee and the following dose modification (see Section 7.2.3). Documented routine neurological exam performed within 6 weeks of randomization is acceptable and does not need to be repeated in Screening.

9.5.7 Audiometric Testing

Audiometric assessments should be performed by a qualified audiologist or qualified designee for all participants at Screening (within 6 weeks prior to randomization). The procedure used for the conduct of the audiometric examination may be conducted according to local institutional practice. If auditory symptoms develop after the Screening assessment and prior to randomization, the audiometric assessments should be repeated prior to randomization. Additional comprehensive audiometric assessments should be conducted as deemed appropriate by the audiologist or qualified designee and following local cisplatin product label to provide continued safety assessment (See also, Section 2.0 – Schedule of Activities). Documented routine audiometric testing performed within 6 weeks of randomization is acceptable and does not need to be repeated in Screening.

9.5.8 Fiber Optic Examination

At screening, fiber optic examination (under general anesthesia, as appropriate) of the upper-aerodigestive tract (with biopsies of the primary lesions(s) if clinically indicated) is required as a baseline exam for all patients. Documented routine fiber optic exam performed within 6 weeks of randomization is acceptable and does not need to be repeated in Screening. While on study treatment, if clinically indicated based on investigator assessment, fiber optic examination of primary tumor site will be performed (under general anesthesia, as appropriate) of the upper-aerodigestive tract with biopsies of the primary lesion(s) and any suspicious lesions. Photographs of the lesion(s) should be routinely performed to ease GTV delineation, if clinically indicated.

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

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (from pre-study to post-study visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in the Study Vendor Manual. Refer to the Schedule of Activities (Section 2) for the timing of laboratory assessments.

Only safety labs affecting potential treatment must be reviewed prior to study therapy administration following the Screening Visit. Labs that would not affect potential treatment of the participant can be reviewed, in a timely manner, by an investigator after the date of study therapy administration. Similarly, if a site is unable to obtain the thyroid function testing (thyroid stimulating hormone [TSH], Free T3 and Free T4) results prior to scheduled dosing, review of the thyroid function test results after dosing is acceptable and poses no additional immediate safety risk to participants.

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

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2. All laboratory tests to determine eligibility and Drug-Induced Liver Injury (DILI) (see Section 5.1 – Entry Criteria [Table 1] and Section 9.3.7 – Events of Clinical Interest, respectively) are mandatory; all other additional laboratory tests are recommended and may be performed according to local institutional standard.

9.5.9.2 Pregnancy Test

- Pregnancy testing for WOCBP:
  - Pregnancy testing requirements for study inclusion are described in Section 6.1.
  - Pregnancy test is required to be repeated within 24 hours prior to starting RT ± cisplatin adjuvant treatment.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention and at the end of treatment.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted for the time required to eliminate systemic exposure after the last dose of each study intervention(s) as noted in Section 6.1. The length of time required to continue pregnancy testing for each study intervention is as follows:
    - Pembrolizumab: 120 days
    - Cisplatin: 180 days
    - Radiotherapy: 180 days
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study. Refer to Appendix 8 for UK-, Germany-, and France-specific requirements.

9.5.9.3 HIV, HBV and HCV Serology

Screening tests are not required unless mandated by local regulations. HIV, HBV, and HCV serology will be conducted on participants per local regulations and site SOPs. Active Hepatitis B is defined as a known positive HBsAg result. Active Hepatitis C is defined by a known positive Hep C Ab result and known HCV RNA results greater than the lower limits of detection of the assay. Refer to Appendix 8 for Germany-specific requirements for HIV, HBV, and HCV testing.

9.6 Pharmacokinetics

Pharmacokinetic samples are not collected in this trial.

9.6.1 Blood Collection for RNA Analysis and Plasma and Serum Biomarker Analyses

Blood should be drawn according to the collection schedule for all participants (Section 2.0). Leftover RNA, plasma, and serum will be stored at the end of the study for FBR if the participant has consented (see Section 9.8). Further details are provided in the Vendor Manual.

9.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

9.8 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of Future Biomedical Research:

- DNA for future research
- Leftover RNA from RNA analyses
- Leftover plasma from plasma biomarker analyses
- Leftover serum from serum biomarker analyses
- Leftover plasma from ctDNA
- Leftover main study tumor

9.9 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA:

- Blood for Genetic Analysis
- Blood for RNA Analysis

- Blood for Serum Biomarker Analysis
- Blood for Plasma Biomarker Analysis
- Blood for ctDNA Analysis
- Tissue Collection for Biomarker Analysis

9.9.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be obtained pre-dose 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 provided in the Vendor Manual. Samples should be collected for planned analysis of associations between genetic variants in germline/tumor DNA and drug response. If a documented law or regulation prohibits (or local IRB/Independent Ethics Committee [IEC] does not approve) sample collection for these purposes, then such samples should not be collected at the corresponding sites. Leftover DNA extracted from planned genetic analysis samples will be stored for FBR only if participant provides documented informed consent for FBR.

9.10 Visit Requirements

Visit requirements are outlined in Section 2 – Schedule of Activities (SoA). Specific procedure-related details are provided above in Section 9 – Study Assessments and Procedures.

9.10.1 Screening

Approximately 28 days prior to treatment randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 6.1. Screening procedures may be repeated after consultation with the Sponsor.

Documented informed consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the participant providing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior randomization except for the following:

- Laboratory tests are to be performed within 10 days prior to randomization. An exception is hepatitis testing which may be done up to 28 days prior to randomization.
- Evaluation of ECOG performance status is to be performed within 10 days prior to randomization.
- For WOCBP, a urine or serum pregnancy test will be performed within 24 hours (urine) or within 72 hours (serum) before randomization. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

- For cases where newly obtained tumor sample is collected within 90 days of randomization, tumor sample collection is not required to be obtained within 28 days prior to randomization for PD-L1 testing for all participants and for HPV p16 testing for participants with oropharyngeal cancers.

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria after consultation with the Sponsor. 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.

After screening, eligible participants will be randomly assigned to treatment. Sites will contact the participants to advise them on their assigned treatment arm and schedule the first post-screening visit as determined by their assigned treatment arm.

9.10.2 Treatment Periods

Visit requirements are outlined in the Schedule of Activities (Section 2.0). Specific procedure-related details are provided in Section 9.1.

In the Neoadjuvant Treatment Phase, there are 2 treatment arms: Arm A/pembrolizumab and Arm B/SoC (no neoadjuvant). Post-definitive surgery, participants will receive adjuvant treatment with RT ± cisplatin plus pembrolizumab in Arm A and without pembrolizumab in SoC arm (Arm B), as assigned during randomization. No crossover from SoC to pembrolizumab will be permitted. Participants who subsequently receive any anticancer treatment not specified in the protocol will discontinue study treatment and enter Follow-up; any treatment would be considered post-study anticancer treatment.

9.10.2.1 Neoadjuvant Treatment (Treatment 1)

Only participants in Treatment Arm A/pembrolizumab will receive neoadjuvant pembrolizumab; participants in Treatment Arm A/pembrolizumab should proceed to surgery directly following the presurgery visit (within 6 weeks [±10 days]) after randomization). Participants in Arm A are allowed to go to surgery outside this timeframe if delays are due to an AE. Participants with delays other than for an AE may be considered with sponsor consultation. Participants in the Treatment Arm B/SoC will proceed directly to surgery following within 4 weeks after randomization.

Visit timing requirements during the treatment period for Arm A are as follows:

- Assessments/procedures should be performed on Day 1 for each cycle.
- Pembrolizumab treatment cycles are 3 weeks (21 days).
- The window for each visit is ± 3 days, unless otherwise noted. Cycle 1 treatment should begin within 3 days of randomization or as close as possible to that date on which the participant is allocated or assigned.

9.10.2.2 Definitive Surgery

All participants will have presurgical assessments performed at Week 0-4 (± 10 days) for the SoC arm (Arm B) or Week 6 (± 10 days) for the pembrolizumab arm (Arm A), to allow assessment of disease status, PROs and safety monitoring. The window for this visit allows participants to proceed to surgery up to 10 days earlier or later if deemed necessary by the investigator.

Definitive surgery will be performed as per local SoC (Arm B/SoC) and following completion of neoadjuvant treatment (Arm A/pembrolizumab). Note: Participants in the pembrolizumab arm (Arm A) may proceed to surgery after 1 dose of pembrolizumab, if deemed appropriate, if the investigator has documented clinical evidence of tumor progression, preferably supported by radiographic evidence.

Participants who do not undergo surgery as originally planned may proceed directly to Treatment 2 and receive salvage RT plus cisplatin ± pembrolizumab, depending on treatment assignment at the discretion of the investigator in consultation with the Sponsor.

9.10.2.3 Post-surgery Safety Follow-up

The mandatory Post-surgery Safety Follow-up Visit should be conducted approximately 7 to 30 days post-surgery. All AEs that occur post-surgery and prior to the Post-surgery Safety Follow-up Visit should be recorded. Section 9.3.1 details the reporting requirements for AEs and SAEs considered to be post-surgical complications by the investigator. Complications and mortality as a consequence of the surgical procedures will be reported as per other AEs and SAEs (see Section 9.1.10.2.3).

Participants considered to have adequately recovered from surgery may proceed directly to adjuvant treatment.

9.10.2.4 Adjuvant Treatment (Treatment 2)

The post-surgery adjuvant treatment period (Treatment 2) is expected to start when participants have recovered adequately from the morbidity and/or complications from the surgery and with RT ± cisplatin commencing at a recommended minimum range of within 6 weeks after definitive surgery. If performed outside of this window, Sponsor consultation will be required. If the start of RT is delayed, up to 4 doses of pembrolizumab may be given. The timing of this dose of pembrolizumab can be adjusted based on timing of surgery after discussion with the Sponsor. The first dose of pembrolizumab given during radiation therapy should be given such that pembrolizumab continues to be given every 21 +/- 3 days.

9.10.3 Post-Treatment Visit

Post-treatment visit requirements are outlined in the Schedule of Activities (Section 2.4).

9.10.3.1 End of Treatment Visit

The End of Treatment visit should occur at the time study treatment is discontinued for any reason. If the End of Treatment visit occurs 30 days from the last dose of study treatment, at the same time as the mandatory 30-Day Safety Follow-up visit, the End of Treatment visit procedures and any additional Safety Follow-up procedures can be combined into a single visit.

Participants who discontinue study treatment for a reason other than disease progression will still be considered on study and should continue with regularly scheduled assessments (also refer to Section 8.1), including collecting participant information on the start of new anticancer therapy, disease progression, and death.

9.10.3.2 Safety Follow-up Visit

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

Reporting requirement for post-treatment follow-up of treatment-related late toxicities meeting serious criteria is detailed in Section 9.3.1.

9.10.3.3 Follow-up Visits

Participants who complete study treatment or discontinue study treatment for a reason other than an event/disease progression/recurrence will move into the Post-Treatment Follow-up Phase and should be assessed in office every 3 months (91 ± 7 days) until the end of Year 3 (measured from the date randomization) to monitor disease status. In Years 4 and 5, participants should be assessed in office every 6 months (182 ± 14 days) to monitor disease status. After Year 5, participants will move into Survival Follow-up. Any additional tests/investigations or imaging assessments for progressive/recurrent disease or safety will be at the discretion of participant's treating physician per local SoC. Every effort should be made to collect information regarding disease status until an event/disease progression, death, withdrawal of consent or end of study. Information regarding post-study anticancer treatment will be collected if new treatment is initiated. Participants who have completed all efficacy assessments must enter Survival Follow-up. Participants who discontinue efficacy assessments early, and have not experienced an event/progression, will be requested for standard of care imaging assessments/biopsy to evaluate disease status.

For a participant who dies during the Follow-up period, date and cause of death should be recorded in the appropriate eCRF.

Participants in Post-Treatment Follow-up will be followed for treatment-related late toxicities for up to Year 5 and should be recorded.

9.10.3.4 Survival Follow-up

All participants who complete Post-Treatment Follow-up, experience an event or disease progression/recurrence verified by BICR will move into the Survival Follow-up Phase and should be contacted by telephone every 3 months (91 ± 14 days) 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 study treatment and who will not enter the Post-Treatment Follow-up Phase, the first survival follow-up contact will be scheduled 3 months (91 ± 14 days) after the End of Treatment Visit and/or Safety Follow-up Visit (whichever is last).
- For participants who completed assessments in the Post-Treatment Follow-up Phase, the first survival follow-up contact will be scheduled 3 months (91 ± 14 days) after the last efficacy assessment follow-up visit has been performed.

The Sponsor may request survival status to be assessed at additional time points during the course of the study. For example, survival status may be requested prior to the eDMC safety review, efficacy IAs and final analysis. All participants who are in the Survival Follow-up Phase and not known to have died prior to the request for these additional survival status time points will be contacted at that time.

9.10.4 Participants Discontinued From Study Treatment but Continuing to be Monitored in the Study

Participants who discontinue study treatment for reasons other than an event/disease progression/recurrence will enter Safety and Post-Treatment Follow-up and undergo all assessments at the scheduled time points are per the Schedule of Activities (Section 2.4) as described in Sections 9.10.3.2, 9.10.3.3 and 9.10.3.4.

Participants that discontinue study treatment due to an event/disease progression/recurrence will enter Safety Follow-up and then proceed directly to Survival Follow-up as described in Section 9.10.3.4 (refer to Sec 8.1 – Discontinuation of Study Treatment). Participants who discontinue study treatment because of the start of new anticancer treatment will enter Safety Follow-up and then proceed directly to Follow-up as described in Section 9.10.3.3.

10 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analysis, will be documented in a supplemental Statistical Analysis Plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Separate analysis plans may be developed for biomarker

analysis and genetic data analysis. Post-hoc exploratory analyses will be clearly identified in the Clinical Study Report. The PRO analysis plan will also be included in the sSAP.

10.1 Statistical Analysis Plan Summary

Key elements of the Statistical Analysis Plan are summarized below; the comprehensive plan is provided in Sections 10.2 to 10.12.

Study Design Overview	A Phase III, Randomized, Open-label Study to Evaluate Pembrolizumab as Neoadjuvant therapy and Pembrolizumab plus Radiotherapy with and without Chemotherapy as Adjuvant Therapy for Stage III-IVA Resectable Locoregionally Advanced Head and Neck Squamous Cell Carcinoma (LA HNSCC)
Treatment Assignment	In this study, 714 participants have been enrolled, which will result in approximately 462 participants whose tumors express PD-L1 CPS≥10 (based on a prevalence rate of ~65% of the CPS≥10 participants among all participants) and approximately 680 participants whose tumors express PD-L1 CPS≥1 (based on a prevalence rate of ~95% of the CPS≥1 participants among all participants) will be randomized in a 1:1 ratio between 2 treatment arms: 1. Pembrolizumab as neoadjuvant therapy and in combination with RT ± cisplatin as adjuvant therapy after surgical resection (referred as pembrolizumab arm) 2. No neoadjuvant therapy and RT ± cisplatin as adjuvant therapy after surgical resection (referred as SoC arm) This study will be conducted as an open-label study. Stratification factors are as follows: • Primary tumor site (oropharynx/oral cavity vs. larynx vs. hypopharynx) • Tumor Stage: III vs. IVA • PD-L1 status (TPS ≥ 50% vs. TPS<50%) This study will be conducted as an open-label study.
Analysis Populations	Efficacy: Intention-to-Treat (ITT) Safety: All Participants as Treated (APaT) PRO: Full Analysis Set (FAS)
Primary Endpoint(s)	Event-free survival (EFS)
Secondary Endpoint(s)	1. Major pathological response (mPR) 2. Overall survival (OS) 3. Pathological complete response (pCR)

Statistical Methods for Key Efficacy Analyses	The primary hypothesis for EFS and key secondary hypothesis for OS will be evaluated by comparing the pembrolizumab arm to the SoC arm using a stratified log-rank test. Estimation of the HR will be done using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method. The key secondary hypothesis for mPR will be evaluated by comparing the pembrolizumab arm to the SoC arm with respect to the rate of mPR using the stratified Miettinen and Nurminen method with strata weighting by sample size. The between-treatment difference in percentages, its 95% CI and p-value 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, the analyses will be provided using the Miettinen and Nurminen (M&N) method [Miettinen, O. and Nurminen, M. 1985].
Interim Analyses	**Efficacy:** Two IAs will be performed. Results will be reviewed by an eDMC. These IAs and the final analysis (FA) are summarized below. Details are provided in Section 10.7. CCI [redacted] **Safety:** An interim safety analysis will be performed and reviewed by the eDMC when the first 15 participants in the pembrolizumab arm have completed RT during the post-surgery adjuvant treatment phase. Afterwards, the eDMC will review safety data periodically in the study.

Multiplicity	CCI [redacted]
Sample Size and Power	The planned sample size is 714 participants, which will result in approximately 462 participants whose tumors express PD-L1 CPS≥10 and approximately 680 participants whose tumors express PD-L1 CPS≥1. CCI [redacted]

10.2 Responsibility for Analyses/In-House Blinding

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

The Sponsor will generate the randomized allocation schedule(s) for study treatment assignment for this protocol, and the randomization will be implemented in IVRS.

Although the study is open-label, analyses or summaries generated by randomized treatment assignment and actual treatment received will be limited and documented. Further documentation will be provided in the sSAP. The central pathologists interpreting surgical specimens for assessment of mPR and pCR will be blinded to treatment assignment. In addition, the independent radiologist(s) will perform the central imaging review without knowledge of treatment group assignment.

Blinding issues related to the planned interim analyses are described in Section 10.7.

10.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 4.0.

10.4 Analysis Endpoints

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

10.4.1 Efficacy Endpoints

10.4.1.1 Primary Efficacy Endpoint

- **Event-free survival (EFS):** the time from randomization to the first of the following events:
  - Radiographic disease progression per RECIST 1.1.

    Exception:
    - Participants who undergo a definitive biopsy of the progressed lesion and are found to have no histologic evidence of invasive cancer will not meet criteria for an event.
  - Radiographic disease progression during neoadjuvant phase that precludes surgery will be considered an event.
  - Local or distant progression or recurrence (as assessed with imaging or biopsy as indicated).
  - Death due to any cause.

A secondary malignancy is not considered an EFS event.

See Section 10.6.1 for definition of censoring.

10.4.1.2 Secondary Efficacy Endpoints

- **Major Pathological Response (mPR):** having ≤ 10% invasive squamous cell carcinoma within the resected primary tumor specimen and all sampled regional lymph nodes as assessed by blinded central pathologists.
- **Overall survival (OS):** the time from randomization to death due to any cause.
- **Pathological Complete Response (pCR):** having no residual invasive squamous cell carcinoma within the resected primary tumor specimen and all sampled regional lymph nodes as assessed by blinded central pathologists.

10.4.2 Safety Endpoints

Safety measurements are described in Section 5.4.1.2 Safety Endpoints and Section 9.5.

10.4.3 Patient Reported Outcome (PRO) Endpoints

The following key PRO endpoints will be evaluated as described in Section 5.4.1.3:

- Global health status/QoL and physical functioning scores from the EORTC QLQ-C30

- Symptom sub-scale and single item scores from the EORTC QLQ-H&N35 including the following:
  - problems with swallowing
  - problems with speech
  - pain in the mouth

Additional scales of the EORTC QLQ-C30/QLQ-H&N35 and exploratory PRO endpoints as described in Section 5.4.1.3 will be evaluated. Details will be provided in the sSAP.

10.5 Analysis Populations

10.5.1 Efficacy Analysis Population

The Intention-to-Treat (ITT) population will serve as the primary population for efficacy analyses in this study, which consists of all randomized participants. Participants will be included in the treatment group to which they are randomized for the analysis of efficacy data using the ITT population.

10.5.2 Safety Analysis Population

Safety analyses will be conducted in the All Participants as Treated (APaT) population, which consists of all randomized participants who received study treatment (note that surgery is part of study treatment). Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who take incorrect study treatment for the entire treatment period; such participants will be included in the treatment group corresponding to the study treatment actually received.

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

10.5.3 Patient Reported Outcome Analysis Population

The PRO analyses are based on the PRO full analysis set (FAS) population, defined as participants who have received treatment and have at least one PRO assessment available.

10.6 Statistical Methods

10.6.1 Statistical Methods for Efficacy Analyses

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

Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 10.8, Multiplicity. Nominal p-values

may be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity.

The 3 stratification factors used for randomization, including primary tumor site, tumor stage, and PD-L1 status defined by TPS 50% will be applied to all stratified analyses; in particular, stratified log-rank test, stratified Cox model, and stratified Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. For participants who were randomized prior to Amendment 04 without stratification factor for PD-L1 status at randomization, the TPS raw score will be used retrospectively to derive the stratification factor for PD-L1 status in the analyses. In the event that there are small strata, for the purpose of analysis, strata will be combined to ensure sufficient number of participants, responses or events in each stratum. Details regarding the pooling strategy will be pre-specified in the sSAP prior to the database lock for [redacted], based on a blinded review of participants and event counts by stratum.

10.6.1.1 Event-Free Survival

The non-parametric Kaplan-Meier method will be used to estimate the EFS curve in each treatment group. The treatment difference in EFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard (PH) model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 7.3) will be applied to both the stratified log-rank test and the stratified Cox model.

Since disease progression/recurrence is assessed periodically, disease progression/recurrence can occur any time in the time interval between the last assessment where the event was not documented and the assessment when the event is first documented. The true date of disease progression/recurrence will be approximated by the date of the first assessment at which the event is objectively documented. Death is always considered as an event. Participants who do not experience a disease progression/recurrence event will be censored at the last disease assessment. Sensitivity analyses will be performed for comparison of EFS based on investigator's assessment.

In order to evaluate the robustness of the EFS endpoint, 1 primary and 1 sensitivity analyses with a different set of censoring rules will be performed. The primary analysis follows the Intention-To-Treat principle. That is, PDs/ recurrences/deaths are counted as events regardless of missed study visits or initiation of new anticancer therapy. For the sensitivity analysis, if the events (disease progression, recurrence or death) are immediately after more than 1 missed disease assessment, the data are censored at the last disease assessment prior to missing visits. Also data after new anticancer therapy are censored at the last disease assessment prior to the initiation of new anticancer therapy. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for primary and sensitivity analyses are summarized in Table 13.

Table 13 Censoring Rules for Primary and Sensitivity Analyses of EFS

Situation	Primary Analysis	Sensitivity Analysis
Disease progression, recurrence, or death documented after ≤ 1 missed disease assessment and before new anticancer therapy, if any	EFS event at date of documented disease progression, recurrence, or death	EFS event at date of documented disease progression, recurrence, or death
Disease progression, recurrent or death documented immediately after ≥ 2 consecutive missed disease assessments or after new anticancer therapy, if any	EFS event at date of documented disease progression, recurrence, or death	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed visits and new anticancer therapy, if any
No disease progression, no recurrence and no death; and new anticancer therapy is not initiated	Censored at last disease assessment	Censored at last disease assessment
No disease progression, no recurrence and no death; new anticancer therapy is initiated	Censored at last disease assessment	Censored at last disease assessment before new anticancer therapy
Abbreviations: EFS = event-free survival		

10.6.1.2 Major Pathological Response

mPR rate is defined as the proportion of participants with an mPR. The stratified Miettinen and Nurminen's method with strata weighting by sample size will be used for the comparison of mPR rates between the pembrolizumab arm and SoC arm. The stratification factors used for randomization (see Section 7.3) will be applied to the stratified Miettinen and Nurminen's method.

Participants who are discontinued from the study treatment and continue with other neoadjuvant treatment not specified by the study prior to definitive surgery will be classified as not having an mPR (non-responders) in the efficacy analyses, regardless of the results obtained from the surgery. Participants who are discontinued from study treatment due to the reasons that preclude surgery are considered non-responders.

10.6.1.3 Overall Survival

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox PH model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR). The HR and its 95% CI from the stratified Cox PH model with Efron's methods of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 7.3) will be applied to both the stratified log-rank test and the stratified Cox model.

10.6.1.4 Pathological Complete Response

pCR rate is defined as the proportion of participants with a pCR. The same method used to analyze mPR rate will be used to analyze pCR rate.

10.6.1.5 Summary of Efficacy Analysis Methods

Table 14 summarizes the primary analysis approach for primary and secondary efficacy endpoints.

Table 14 Analysis Strategy for Primary and Secondary Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method[†]	Analysis Population	Missing Data Approach
Primary:			
EFS	Test: stratified Log-rank test Estimation: stratified Cox model with Efron's tie handling method	ITT • Participants whose tumors express PD-L1 CPS≥10 • Participants whose tumors express PD-L1 CPS≥1 • All participants	• Primary censoring rule • Sensitivity analysis 1 (More details are in Table 13)
Secondary:			
mPR	Stratified M&N method	ITT • Participants whose tumors express PD-L1 CPS≥10 • Participants whose tumors express PD-L1 CPS≥1 • All participants	Participants with relevant data missing are considered non-responders
OS	Test: stratified Log-rank test Estimation: stratified Cox model with Efron's tie handling method	ITT • Participants whose tumors express PD-L1 CPS≥10 • Participants whose tumors express PD-L1 CPS≥1 • All participants	Censored at last date participant was known to be alive
pCR	Stratified M&N method	ITT • Participants whose tumors express PD-L1 CPS≥10 • Participants whose tumors express PD-L1 CPS≥1 • All participants	Participants with relevant data missing are considered non-responders

[†] Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization (see Section 7.3.1 – Stratification) will be applied to the analysis model.
Abbreviations: CPS = combined positive score; EFS = Event-free survival; ITT = Intention-To-Treat; M&N = Miettinen and Nurminen; mPR = major pathological response; OS = overall survival; pCR = pathological complete response; PD-L1 = programmed cell death ligand 1.

10.6.2 Statistical Methods for Safety Analyses

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

The overall safety evaluation will include a summary of the number and percentage of participants with at least one AE, drug-related, SAE, serious drug-related AE, Grade 3-5 AE, drug-related Grade 3-5 AE, discontinuation from study intervention due to an AE, 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 treatment groups 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 in the percentage of participants with specific Grade 3-5 AEs (≥5% of participants in any treatment group) and SAEs (≥5% of participants in any treatment group) will also be summarized by point estimate and 95% CI. Rainfall plots with point estimates and 95% CIs will be displayed for 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 V4.0 for each gradable laboratory test. For continuous safety measures, such as change from baseline in laboratory and vital signs, summary statistics for baseline, on-treatment, and change from baseline values will be provided.

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 15 Analysis Strategy for Safety Parameters

Analysis Part	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Overall Safety Assessment	Specific Grade 3-5 AE (incidence ≥5% of participants in one of the treatment groups)	X	X
	Specific serious AE (incidence ≥5% of participants in one of the treatment groups)	X	X
	Specific AEs, SOCs (incidence ≥10% of participants in one of the treatment groups)	X	X
	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 Grade3-5 and Drug-Related AE		X
	Discontinuation due to AE		X
	Death		X
	Specific AEs, SOCs (incidence > 0% of participants in all of the treatment groups)		X
	Change from Baseline Results (lab toxicity shift)		X
Assessment of safety topics of special interest	Pembrolizumab AEOSI		X

Abbreviations: AE = adverse event; AEOSI = adverse event of special interest; CI = confidence interval; SOC = system organ class.

10.6.3 Statistical Methods for Patient Reported Outcome Analyses: EORTC QLQ-C30 & QLQ-H&N35

Change from baseline (the Treatment 1 Cycle 1 assessment in the pembrolizumab arm and the presurgery assessment in the SoC arm) in the following secondary QoL outcomes will be assessed:

- EORTC QLQ-C30 Global health status/QoL score
- EORTC QLQ-C30 Physical functioning score
- QLQ- H&N35 Swallowing symptom score
- QLQ- H&N35 Speech symptom score
- QLQ-H&N35 Pain symptom score

To assess the treatment effects on the QoL outcomes, a constrained longitudinal data analysis model will be applied, with the PRO score as the response variable, and treatment, time, the treatment by time interaction and stratification factors as covariates. The least square mean change from baseline will be summarized for each outcome. The short-term treatment effect on PRO score change from baseline in the pembrolizumab arm will be evaluated during neoadjuvant treatment and at the presurgery assessment. The long-term treatment effect on PRO score change from baseline will be primarily evaluated and compared in both treatment arms approximately 6 and 12 months following the completion of RT ± cisplatin.

Details of PRO analyses will be described in the sSAP.

10.6.4 Summaries of Baseline Characteristics and Demographics

The 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 reason for screening failure and discontinuation will be displayed. Demographic variables (eg, age, race, etc.), baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables.

10.7 Interim Analyses

There are 2 planned IAs. Access to the allocation schedule for summaries or analyses for presentation to the eDMC will be restricted to an unblinded statistician and an unblinded scientific programmer performing the interim analysis, who will have no other responsibilities associated with the study.

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

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

10.7.1 Efficacy Interim Analyses

The interim and final analyses strategy for efficacy is summarized in Table 16.

Table 16 CCI [redacted]

CCI [redacted]

Decisions to stop the study early will be based on DMC recommendations with review by the Executive Oversight Committee. In the event that the study is stopped early for efficacy, the study will continue to follow participants for survival update.

Type I error control for the efficacy analyses as well as efficacy bounds are described in Section 10.8 Multiplicity.

10.7.2 Safety Interim Analyses

The DMC will be responsible for periodic interim safety reviews. An interim safety analysis will be performed when the first 15 participants in the pembrolizumab arm have completed RT during the post-surgery adjuvant treatment phase (approximately 5 months since first participant is randomized). Afterwards, the DMC will review safety data periodically in the study. Safety IAs will also be performed at the time of efficacy IAs. Details will be specified in the DMC charter.

The interim analyses strategy for safety is summarized in Table 17.

Table 17 Summary of Interim Analyses Strategy for Safety

Key Endpoints	Timing	Estimated Months after First Participant Randomized	Primary Purpose of Analysis
• AEs • Surgical delays	• First 15 participants in the pembrolizumab arm have completed RT during the post-surgery adjuvant treatment phase • Periodic interim safety reviews thereafter	• ~5 months • As specified in the DMC charter	Safety evaluation

Abbreviations: AE = Adverse Event; DMC = Data Monitoring Committee; RT = Radiotherapy

10.8 Multiplicity

10.8.1 Multiplicity Control for Efficacy Interim Analyses

CCI

Figure 2 CCI

10.8.1.1 Event-Free Survival

CCI

Table 18 CCI

CCI

Table 19 CCI [redacted]

CCI [redacted]

Table 20 CCI

CCI

CCI

10.8.1.2 Major Pathologic Response

CCI

Table 21 CCI

CCI

10.8.1.3 Overall Survival

CCI

Table 22 CCI [redacted]

CCI [redacted]

CCI [redacted]

Table 23 CCI

CCI

CCI

Table 24 CCI

CCI

[redacted]

10.8.2 Multiplicity Control for Safety Interim Analyses

The DMC has responsibility for assessment of overall risk: benefit. When prompted by safety concerns, the DMC can request corresponding efficacy data. DMC review of efficacy data to assess the overall risk: benefit to study participants will not require a multiplicity adjustment typically associated with a planned efficacy IA. However, to account for any multiplicity concerns raised by the DMC review of unplanned efficacy data when prompted by safety concerns, a sensitivity analysis for OS adopting a conservative multiplicity adjustment will be pre-specified in the sSAP.

10.9 Sample Size and Power Calculations

CCI

[redacted]

CCI

[redacted]

10.10 Subgroup Analyses

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

- Primary tumor site (oropharynx/oral cavity vs. larynx vs. hypopharynx)
- Tumor Stage (III vs. IVA)
- PD-L1 status (TPS ≥ 50% versus TPS<50%)
- Age category (<65 vs. ≥65 years)

- Sex (female vs. male)
- Race (white vs. all others)
- Smoking status (never vs. former vs. current)
- Geographical regions (North America vs. European Union vs. Rest of the World)

The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above, using unstratified methods. In addition, a forest plot will be produced, which provides the estimated point estimates and confidence intervals for the treatment effect across the categories of subgroups listed above. If the number of participants in a category of a subgroup variable is less than 10% of the analysis population, the subgroup analysis will not be performed for this category of the subgroup variable, and the forest plot will not display this category of the subgroup variable.

10.11 Compliance (Medication Adherence)

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

10.12 Extent of Exposure

Extent of exposure for a participant is defined as number of cycles in which the participant receives the study treatment infusion. Summary statistics will be provided on Extent of Exposure for the APaT population.

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12 APPENDICES

Appendix 1: Abbreviations and Trademarks

Abbreviation	Definition
AE	Adverse event
AEOSI	Adverse event of special interest
AJCC	American Joint Committee on Cancer
ALT (SGPT)	Alanine aminotransferase (serum glutamic pyruvic transaminase)
APaT	All participants as treated
aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST (SGOT)	Aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
β-hCG	β-Human chorionic gonadotropin
BICR	Blinded independent central review
CD	Cluster of differentiation
CI	Confidence interval
C_{max}	Maximum serum concentration
COVID-19	Coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CPS	Combined positive score
CrCl	Creatinine clearance
CRF	Case report form
CRT	Chemoradiation or Chemoradiotherapy
CT	Computed tomography
CTCAE	Common terminology criteria of adverse events
ctDNA	Circulating tumor DNA
CTFG	Clinical Trial Facilitation Group
CTLA-4	Cytotoxic T-lymphocyte associated protein 4
C_{trough}	Trough concentration
CTV	Clinical target volume
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
DMFS	Distant metastases-free survival
DOR	Duration of response
ECG	Electrocardiogram
ECI	Events of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eDMC	External Data Monitoring Committee
EEA	European Economic Area
EFS	Event-free survival
EORTC	European Organisation for Research and Treatment of Cancer
ePRO	Electronic patient-reported outcome
EQ-5D-5L	EuroQoL-5 dimension questionnaire
EU CTR	European Union Clinical Trials Regulation
FAS	Full analysis set
FBR	Future biomedical research
FDA	Food and Drug Administration

Abbreviation	Definition
FDG-PET	Fluorodeoxyglucose-positron emission tomography
FFPE	Formalin-fixed paraffin-embedded
FNA	Fine needle aspirate
FSH	Follicular stimulating hormone
FSR	First Site Ready
FU	Follow-up
GCP	Good clinical practice
GFR	Glomerular filtration rate
GTV	Gross tumor volume
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HNC	Head and neck cancer
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
HR	Hazard ratio
IA	Interim analysis
ICF	Informed consent form
ICRU	International Commission on Radiation Units
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IgG4	Immunoglobulin G4
IGRT	Image guided radiation therapy
IMP	Investigational medicinal product
IMRT	Intensity modulated radiation therapy
irAEs	Immune-related adverse events
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
LA	Locoregionally advanced
mAb	Monoclonal antibody
MISP	Merck Investigator Studies Program
mPR	Major pathological response
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
NCI	National Cancer Institute
NSAIDs	Nonsteroidal anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
OAR	Organs at risk
ORR	Objective response rate
OS	Overall survival
PBPK	Physiologically based pharmacokinetic
pCR	Pathological complete response
PD	Progressive disease
PD-1	Programmed cell death 1

Abbreviation	Definition
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PH	Proportional hazard
PK	Pharmacokinetic
po	Per os; oral(ly)
PRO	Patient reported outcome
PRV	Planning organ at risk volume
PTV	Planning target volume
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QA	Quality assurance
QLQ	Quality of life questionnaire
QoL	Quality of life
RECIST	Response evaluation criteria in solid tumors
R/M HNSCC	Recurrent or metastatic head and neck squamous cell carcinoma
RT	Radiotherapy
SAE	Serious adverse event
SAP	Statistical analysis plan
SHP	Src homology region 2 domain-containing phosphatase
SIB-IMRT	Simultaneous integrated boost-intensity modulated radiation therapy
SIM	Site imaging manual
SoA	Schedule of assessments
SoC	Standard of care
SOC	System organ class
SOP	Standard Operating Procedure
sSAP	Supplemental statistical analysis plan
T1DM	Type 1 diabetes mellitus
UICC	Union for International Cancer Control
ULN	Upper limit of normal
US	United States
VOP	Verification of progression
vs.	Versus
WOCBP	Woman of childbearing potential

Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 25 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6.1 and 6.2 of the protocol.
- All laboratory tests to determine eligibility, Drug-Induced Liver Injury (DILI) (see Section 5.1 – Entry Criteria Table 1 and Section 9.3.7 – Events of Clinical Interest, respectively), creatinine clearance prior to cisplatin dosing, and thyroid testing (as specified in footnote f) are mandatory; all other additional laboratory tests are recommended and may be performed according to local institutional standard.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 25 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count	RBC Indices: MCV MCH		WBC count with Differential: Neutrophils Lymphocytes
	RBC Count			
	Hemoglobin			
	Hematocrit			
Chemistry	Blood Urea Nitrogen (BUN)[a]	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the ULN)
	Creatinine	A measure of CO_2 or Bicarbonate[b]	Chloride	Phosphorous
	Creatinine clearance (CrCl)[c] or GFR	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (nonfasting)	Calcium[d]	Alkaline phosphatase	Magnesium
	Albumin			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			

Laboratory Assessments	Parameters
Other Tests	• Serum or urine β human chorionic gonadotropin (β hCG) pregnancy test (for WOCBP according to the requirements in Section 6.1 and Section 9.5.9.2). Refer to Appendix 8 for UK-, Germany-, and France-specific requirements. • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) testing is not required unless mandated by local health authority. If required, testing will be conducted per local regulations and site SOPs. Refer to Appendix 8 for Germany-specific requirements. • Prothrombin (PT) or International normalized ratio (INR) • Activated partial thromboplastin time (aPTT)[e] • Free triiodothyronine (FT3)[f] • Free thyroxine (FT4)[f] • Thyroid stimulating hormone (TSH)
NOTES: CrCl = creatinine clearance; GFR = glomerular filtration rate; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; RBC = red blood cell; SOPs = Standard Operating Procedures; ULN = upper limit of normal; WBC = white blood cell; WOCBP = women of childbearing potential. a. BUN is preferred; if not available urea may be tested. b. If available as standard of care in your region. The carbon dioxide may be either a measurement of CO_2 or bicarbonate as an electrolyte. c. CrCl should be calculated per institutional standard. CrCl to be repeated within 3 days prior to start of each cisplatin administration for management of dose reduction for renal toxicity guidelines. d. Corrected calcium should be checked for participants with hypoalbuminemia. e. PTT may be performed if the local laboratory is unable to perform aPTT. f. In case of elevated TSH, add Free T3 and Free T4. Free T4 should be performed on all participants with elevated TSH; Free T3 only needs to be performed if it is done as a part of local standard of care. If the Free T3 and Free T4 are not available locally, they can be sent to the central laboratory to be performed (see Laboratory Manual for details).	

Investigators must document their review of each laboratory safety report.

Appendix 3: Regulatory, Ethical, and Study Governance Considerations

Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)
Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

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

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

Financial Disclosure

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

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 institutional review board, ethics review committee (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 trial 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.

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 trial documents in order to verify worksheet/case report form data. By signing the consent form, the participant agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

Confidentiality of IRB/IEC Information

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

Committees Structure

Scientific Advisory Committee

This trial was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

Trial Steering Committee

This trial will be conducted in consultation with a Trial Steering Committee. The Trial Steering Committee comprises:

- Sponsor personnel
- Investigators participating in the trial
- Consulting therapeutic-area experts and clinical trialists

The Trial Steering Committee will provide guidance on the operational aspects of the trial.

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

Executive Oversight Committee

The Executive Oversight Committee (EOC) comprises members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the Data Monitoring Committee (DMC) or Trial Steering Committee regarding the trial.

Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an external Data Monitoring Committee (DMC) will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the DMC must not

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

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 10.7 - Interim Analyses) and recommend to the EOC if the trial 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 external collaborating organization protocol team; meeting facilitation; the trial 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.

Publication Policy

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

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

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries.

Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

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 MSD 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 trial reimbursed to the investigator by the Sponsor.

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

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 trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial 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.

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.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial 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 regulatory authority as a result of an audit or inspection to cure deficiencies in the trial documentation and worksheets/case report forms.

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.

Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. 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 may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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 trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of Medication Error, Misuse, and Abuse

Medication Error
● This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.
Misuse
● This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.
Abuse
● This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product for a perceived psychological or physiological reward or desired non-therapeutic effect.

Definition of AE

AE Definition
● An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. ● 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 treatment. ● NOTE: for purposes of AE definition, study treatment includes any pharmaceutical product, biological product, vaccine, device, diagnostic agent or protocol specified procedure whether investigational (including placebo or active comparator product) or marketed, 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, or are considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment 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 treatment or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated adverse event, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer (that is not a condition of the study).

  Note: Progression of the cancer under study is not a reportable event. Refer to Section 9.3.5 for additional details.

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to section 9.3.5 for protocol specific exceptions

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

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening ● The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization ● Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a MSD product and is documented in the patient'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) which 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 one 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.

Additional Events reported in the same manner as SAE

Additional Events which require reporting in the same manner as SAE
● In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe 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.

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

Assessment of Intensity

- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.
  - Grade 1: Mild; asymptomatic or mid 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 or hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

Assessment of Causality

- Did the study intervention cause the adverse event?
  - The determination of the likelihood that the study intervention caused the adverse event 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 adverse event based upon the available information
  - **The following components are to be used to assess the relationship between the study intervention and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the adverse event:
    - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
    - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials 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 study intervention discontinued or dose/exposure/frequency reduced?
  - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
  - If no, this is a negative dechallenge.

  (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the study intervention; (3) the trial is a single-dose drug trial); or (4) study intervention (s) is/are only used one time.)
- **Rechallenge:** Was the participant re-exposed to the study intervention in this trial?
  - 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 trial is a single-dose drug trial); or (3) study intervention (s) is/are used only one time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE STUDY INTERVENTION, OR IF RE-EXPOSURE TO THE STUDY INTERVENTION POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.

- **Consistency with Study treatment Profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship: There is evidence of exposure to the study intervention. The temporal sequence of

the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.

- No, there is not a reasonable possibility of study intervention relationship: Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one 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 adverse event 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 adverse event 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.

Reporting of AE, SAE, and Other Reportable Safety Events to the Sponsor

AE, SAE, and Other Reportable Safety Event Reporting to Sponsor via Electronic Data Collection Tool

● The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
  ● Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  ● If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  ● Reference section 9.3.1 – Time Period and Frequency for Collecting AE and SAE and Other Reportable Safety Event Information 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 electronic data collection 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 electronic data collection 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 Trial File Binder (or equivalent).

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

Appendix 5: Contraceptive Guidance and Pregnancy Testing

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

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

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (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 non-hormonal 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.

Contraception Requirements

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in Section 6.1:

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

- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 26 when having penile-vaginal intercourse with a woman of childbearing potential 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 penetration.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 26 during the protocol-defined time frame in Section 6.1.

Table 26 Highly Effective Contraception Methods

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

Pregnancy Testing

Refer to Section 9.5.9.2 for pregnancy testing requirements during the study. Refer to Appendix 8 for UK-, Germany- and France-specific requirements.

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

1. **Definitions**

a. iomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. **Scope of Future Biomedical Research[3, 4]**

The specimens consented and/or collected in this trial as outlined in Section 9.8 – Future Biomedical Research Samples will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. **Summary of Procedures for Future Biomedical Research[3, 4]**

a. Participants for Enrollment

All participants enrolled in the clinical trial will be considered for enrollment in Future Biomedical Research.

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

~~d.~~ Future Biomedical Research Specimen(s)

Collection of specimens for Future Biomedical Research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the participant is having blood drawn for other trial purposes.

4. Confidential Participant Information for Future Biomedical Research[3, 4]

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link participant' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3, 4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in Future Biomedical Research protocol and consent. Future

Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research[3, 4]

Participants may withdraw their consent for Future Biomedical Research and ask that their biospecimens not be used for Future Biomedical Research. Participants may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@msd.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for Future Biomedical Research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the participant’s personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens[3, 4]

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants[3, 4]

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population[3, 4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research[3, 4]

For future biomedical research, risks to the participant have been minimized. No additional risks to the participant have been identified as no additional specimens are being collected for Future Biomedical Research (ie, only leftover samples are being retained).

The Sponsor has developed strict security, policies and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@msd.com.

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf
3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

Appendix 7: Country-specific Requirements

Cisplatin Market Authorization

For France see http://base-donnes-publique.medicaments.gouv.fr for the most recent version of the medicines SmPC.

Appendix 8: Country-specific Protocol Requirements

For United Kingdom:

1. Monthly pregnancy testing is required throughout trial treatment.

Relates to sections:

2 - Schedule of Activities
(2.1 2.2 and 2.3)

9.5.9.2 – Pregnancy Test

Appendix 2 - Clinical Laboratory Tests

Appendix 5 – Contraceptive Guidance and Pregnancy Testing

2. The prohibition against live vaccines is extended to 3 months after the end of study treatment.

Relates to section:

7.7 - Concomitant Therapy

For Germany:

1. Monthly pregnancy testing is required throughout trial treatment and at treatment end for women of childbearing potential.
2. In Treatment Arm A only, a pregnancy test should be completed at the first treatment follow-up visit that takes place at or after 180 days following completion of treatment with pembrolizumab for female participants considered WOCBP.
3. In Treatment Arm B only, female participants considered WOCBP should complete a pregnancy test at the first 2 post-treatment follow-up visits (at 12 weeks ± 7 days after the end of RT ± cisplatin treatment and at the subsequent visit 3 months thereafter (± 7 days).
4. Women of childbearing potential must observe the protocol specified contraceptive guidelines beginning with the first screening visit.

Relates to sections:

2.1 Initial Treatment Phase

2.2 Post-surgery Treatment 2 Phase

2.4 End of Treatment and Follow-up Visits

6.3.4 Contraception

9.5.9.2 Pregnancy Test

Appendix 2: Clinical Laboratory Tests

Appendix 5: Contraceptive Guidance and Pregnancy Testing

5. HIV, Hepatitis B and Hepatitis C testing are required at screening visit.

Relates to sections:

2.0 Schedule of Activities (SoA)

9.5.9.3 HIV, HBV and HCV serology

Appendix 2: Clinical Laboratory Tests

6. Has a known history of human immunodeficiency virus (HIV) infection. HIV testing is required at screening visit.

Relates to section:

6.2 Exclusion Criterion #20

7. Has a known history of or is positive for Hepatitis B (defined as hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C (defined as Hepatitis C virus [HCV] RNA [qualitative] is detected). Hepatitis B and Hepatitis C testing is required at screening visit.

Relates to section:

6.2 Exclusion Criterion #21

8. Prohibited concomitant therapies or vaccinations are prohibited during screening and study treatment phases only.

Relates to section:

7.7 Concomitant Therapy

9. Participants should not receive live vaccines within 30 days prior to randomization or during study treatment.
10. Participants should not receive live vaccines for at least 3 months following the last administered dose of cisplatin. This guidance is applicable for participants in Arm B and for all participants who discontinue earlier than scheduled but had at least 1 treatment with cisplatin.

Relates to section:

7.7 Concomitant Therapy #6

11. Potentially nephrotoxic medications (cephalosporins, amphotericin B or contrast media) which could potentiate a toxic effect of cisplatin on kidney function should be used with caution during cisplatin treatment.
12. Loop diuretics, which could potentiate an ototoxic effect of cisplatin, should be used with caution during cisplatin treatment.

Relates to section:

7.7 Concomitant Therapy #9

13. At time of withdrawal or discontinuation, it is recommended that the investigator counsel the participant on appropriate preventive measures. These measures include avoiding live vaccines within 3 months from the last dose of cisplatin and maintaining contraceptive measures as detailed in Appendix 5.

Relates to sections:

8.1 Discontinuation of Study Treatment

8.2 Withdrawal from the Study

9.1.11 Withdrawal/Discontinuation

For France:

1. Monthly pregnancy testing is required throughout trial treatment and at treatment end for women of childbearing potential.

Relates to sections:

2.1 Initial Treatment Phase

2.2 Post-surgery Treatment 2 Phase

9.5.9.2 Pregnancy Test

Appendix 2: Clinical Laboratory Tests

Appendix 5: Contraceptive Guidance and Pregnancy Testing

2. Be eligible for primary surgery based on investigator decision and per local practice. *This decision must be validated by members of a multidisciplinary team, including the surgical oncologist, medical oncologist, and radiation oncologist.*

Relates to section:

6.1 Inclusion Criterion #2

NOTE: The addition of the italicized text above to criterion #2 has been incorporated into the main protocol body with this global amendment.

3. Subjects with cardiorespiratory disease contraindicating hyperhydration are not allowed in the study.

Relates to section:

6.2 Exclusion Criterion #25

4. Participants with a history of any contraindication to any components of pembrolizumab, RT or cisplatin or their analogs are not allowed.

Relates to section:

6.2 Exclusion Criterion #26

5. The use of phenytoin for seizure prophylaxis is prohibited during the study.

Relates to sections:

6.2 Exclusion Criterion #27

7.7 Concomitant Therapy

6. Requirement for permanent discontinuation of study treatment for:

- Grade 4 skin reaction or confirmed Stevens-Johnson Syndrome or toxic-epidermal necrolysis,
- recurrent Grade 3 colitis, or
- Grade 3 or 4 myocarditis (see Note below).

France-specific additions to Table 3 Dose modification and toxicity management guidelines for immune-related adverse events associated with pembrolizumab.

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow up**
Colitis	Recurrent Grade 3	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with 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.
Rash	Grade 4 skin reaction or confirmed Stevens-Johnson Syndrome or toxic epidermal necrolysis	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	

Relates to section:

7.2.1 Dose Modifications for Pembrolizumab

NOTE: Dose modification and toxicity management guidelines for myocarditis have been incorporated in Table 3 in the main protocol body with this global amendment.

For Japan:

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

Relates to section:

7.1 Treatments Administered, Table 2

Appendix 9: Technical Note for the Poisson Mixture Model and Piecewise Exponential Survival Model

The Poisson mixture model is applied to account for the failure rates decreasing over time in the trial which is a mixture of participants suffering from disease progression/recurrence and others who have excellent long-term results. The survival function as a function of time t for the SoC arm is:

$$S_c(t) = exp(-\theta(1-S_0(t)))$$

where θ = - log (cure rate) and $S_0(t)$ is the survival distribution function for those who suffer from disease progression/recurrence ("not cured"). For this trial, $S_0(t)$ takes the form of a 2-piece piecewise exponential survival function with different hazard functions prior to and post-surgery, respectively.

Given a set of time points $0 = \tau_0 < \tau_1 < \ldots < \tau_{m-1} < \tau_m$, the piecewise exponential survival function takes the following form:

$$S(t) = \exp(-\sum_{l=0}^{m} \lambda_l \int_0^t I_l(s)ds)$$

where λ(t) is the piecewise constant hazard function defined as follows:

$$\lambda(t) = \sum_{l=0}^{m} \lambda_l I_l(t) \qquad \text{with } I_l(t) = \begin{cases} 1 & \text{if } \tau_l \le t < \tau_{l+1} \\ 0 & \text{if elsewhere} \end{cases}$$

The survival function $S_i(t)$ for a given interval $\tau_i \le t < \tau_{i+1}$ simplifies to:

$$S_i(t) = \exp(-\sum_{l=0}^{i-1} \lambda_l(\tau_{l+1} - \tau_l) - \lambda_i(t - \tau_i))$$