Official Protocol Title:	A Randomized Phase III study of pembrolizumab given concomitantly with chemoradiation and as maintenance therapy versus chemoradiation alone in subjects with locally advanced head and neck squamous cell carcinoma (KEYNOTE-412)
NCT number:	NCT03040999
Document Date:	21-Nov-2022

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

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Rahway, NJ 07065 USA

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

TITLE:

A Randomized Phase III study of pembrolizumab given concomitantly with chemoradiation and as maintenance therapy versus chemoradiation alone in subjects with locally advanced head and neck squamous cell carcinoma (KEYNOTE-412)

IND NUMBER: 122,325

EudraCT NUMBER: 2016-003934-25

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 08 – Global amendment	21-NOV-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address. Additionally, scheduled trial assessments/procedures were modified based on the results of the final efficacy analysis.
Amendment 07 – Global amendment	16-DEC-2020	1) To update the assumptions of the survival distribution of the control arm based on emerging data from JAVELIN 100; and to update the timing of efficacy analysis to allow for additional follow-up of all subjects. 2) To allow imaging assessments to continue for subjects who have not experienced an event. Censoring rules have been changed accordingly. 3) Collection of FDG-PET reports and corresponding imaging (CT/MRI) reports to fulfill a regulatory request.
Amendment 06 – Global amendment	30-SEP-2019	1) To align the protocol-specified criteria for locoregional failure with the definition of an event considering that protocol- specified locoregional failures are also clinically significant events. 2) Events in patients with locally advanced head and neck SCC treated with definitive CRT can occur in the absence of radiographic progression per RECIST 1.1 by BICR. Therefore, the EFS definition is being revised accordingly to clarify the scenarios in which histological confirmation of invasive cancer secondary to residual and/or progressive disease fulfills criteria for an event in the absence of radiographic progression per RECIST 1.1 by BICR.
Amendment 05 – France-specific amendment	06-AUG-2018	To align with Keytruda SmPC and regulatory requirements at French sites.

Document	Date of Issue	Overall Rationale
Amendment 04 – Global amendment	26-APR-2018	Updated guidelines for dose modification to align with the most current label and safety information for pembrolizumab.
Amendment 03 – France-specific amendment	13-APR-2017	Revision of inclusion criteria for creatinine clearance to ensure control and management of dose reduction for renal toxicity guidelines per France Health Authority request.
Amendment 02 – Global amendment	26-MAY-2017	Revision of RT dose parameters to ensure standardization and uniformity of treatment for study while providing flexibility for global radiation therapy practices.
Amendment 01 – Germany-Specific amendment	28-FEB-2017	Provision of additional guidance on highly effective contraception as described in CTFG.
Original Protocol	18-NOV-2016	Not Applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 412-08

Overall Rationale for the Amendment:

Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address. Additionally, scheduled trial assessments/procedures were modified based on the results of the final efficacy analysis.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page 12.1 Code of Conduct for Clinical Trials Throughout	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
1.0 Trial Summary	Updated the duration of the trial to 7 years.	Updated the trial duration to allow for additional follow-up.

Section # and Name	Description of Change	Brief Rationale
5.2 Trial Treatment(s) 5.12 Beginning and End of the Trial 7.2.1 Definitions of Medication Error, Misuse, and Abuse	Study intervention table was updated to add IMP/NIMP designations. Added the definition of end of study for the purposes of analysis and reporting. Also, added the definition of local start of the study when a European Economic Area Member State is included. Added a new section with definitions of medication error, misuse, and abuse.	To comply with European Commission regulations.
5.3.2.5 Evaluation of Post-Operative Complications	Deleted the statement about classification of post-operative complications.	All post-operative complications are reported and graded in the same way as other AEs per CTCAE v4.0.
6.1 Trial Screening and Treatment 1 (Pembrolizumab/Placebo + CRT) 6.2 Treatment 2 (Pembrolizumab or Placebo Maintenance) and Post-CRT Follow-up Year 1 6.3 Post-Treatment Efficacy Follow-up Visits 7.1.4.2 FDG-PET	Updated footnotes “t”, “q”, and “l” in Sections 6.1, 6.2, and 6.3, respectively, and Section 7.1.4.2 to specify that post-baseline FDG-PET or FDG-PET/CT reports are no longer required to be collected by the Sponsor.	Collection of PET scan reports no longer required because the final efficacy analysis has been completed.

Section # and Name	Description of Change	Brief Rationale
6.3 Post-Treatment Efficacy Follow-up Visits 7.1.6 Patient Reported Outcomes (PROs)	Updated footnote 'm' in Section 6.3 and added a statement to Section 7.1.6 to indicate that since completion of the final efficacy analysis, any additional ePROs are no longer required to be collected by the Sponsor.	Final efficacy analysis of this endpoint has been completed.
12.1 Code of Conduct for Clinical Trials	Made minor text updates to include diverse and underrepresented groups.	Updated based on inclusion of diverse and underrepresented groups (age, race, ethnicity, gender, etc.) in global clinical studies.
12.10.2 Japan-specific Requirements	Text added to clarify the classification of placebo for infusion per Japanese local regulations.	Added to clarify the category of drug in the clinical trial notification submitting to the regulatory authority.
Throughout the document	Minor typographic and administrative revisions were made.	Minor clarifications, or corrections in spelling or grammatical errors.

1.0 TRIAL SUMMARY

<table>
<tr><td>Abbreviated Title</td><td>Pembrolizumab or placebo in combination with chemoradiation (CRT) in subjects with locally advanced HNSCC</td></tr>
<tr><td>Sponsor Product Identifiers</td><td>MK-3475
Pembrolizumab</td></tr>
<tr><td>Trial Phase</td><td>Phase III</td></tr>
<tr><td>Clinical Indication</td><td>Locally advanced head and neck squamous cell carcinoma (LA HNSCC)</td></tr>
<tr><td>Trial Type</td><td>Interventional</td></tr>
<tr><td>Type of control</td><td>Placebo</td></tr>
<tr><td>Route of administration</td><td>Pembrolizumab/Placebo – intravenous
Cisplatin - intravenous
Radiotherapy Regimen - Standard Fractionation (SFX; Gy) or Accelerated Fractionation (AFX; Gy)</td></tr>
<tr><td>Trial Blinding</td><td>Double-blind</td></tr>
<tr><td>Treatment Groups</td><td>There are two treatment arms:
Pembrolizumab + CRT
Placebo + CRT
<table>
<tr><th>Treatment</th><th>Arm 1</th><th>Arm 2</th></tr>
<tr><td>Pembrolizumab or Placebo</td><td>Pembrolizumab
200 mg</td><td>Placebo</td></tr>
<tr><td>Cisplatin</td><td>100 mg/m^2</td><td>100 mg/m^2</td></tr>
<tr><td>Radiotherapy</td><td>AFX
or
SFX</td><td>AFX
or
SFX</td></tr>
</table></td></tr>
<tr><td>Number of trial subjects</td><td>Approximately 780 subjects will be enrolled.</td></tr>
<tr><td>Estimated duration of trial</td><td>The Sponsor estimates that the trial will require approximately 7 years from the time the first subject (or their legally acceptable representative) provides documented informed consent until the last participant’s last study-related contact.</td></tr>
</table>

Duration of Participation	Each subject will participate in the trial from the time the subject provides documented informed consent form (ICF) through the final protocol-specified contact. After a screening phase of 28 days, each subject will be assigned to receive trial treatment until an event/disease progression is confirmed, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, noncompliance with trial treatment or procedure requirements, administrative reasons requiring cessation of treatment, or until subject has received up to 17 administrations of pembrolizumab/placebo (approximately 1 year). Eligible subjects will be stratified according to 3 stratification factors and will receive a priming dose of pembrolizumab, or placebo followed by chemoradiation (CRT) plus 2 doses of pembrolizumab/placebo over approximately 8 weeks. After completion of CRT, subjects will receive up to a year total (~14 doses) of pembrolizumab/placebo maintenance doses. Subjects will be evaluated for neck dissection at 12 weeks post-CRT. Once trial treatment has completed, subjects will be followed for disease assessment. After the end of treatment, each subject will be followed for the occurrence of adverse events and spontaneously reported pregnancy as described under Section 7.2 of the protocol. Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression/an event is confirmed as per Section 8.4.1.1, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone for overall survival until death, withdrawal of consent or the end of the study.

Randomization Ratio	1:1

A list of abbreviations used in this document can be found in Section 12.3.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a Phase III, randomized, placebo-controlled, double-blind study to determine the efficacy and safety of pembrolizumab given concomitantly with chemoradiation (CRT) and as maintenance therapy versus placebo plus CRT in subjects with locally advanced head and neck squamous cell carcinoma (LA HNSCC) to be conducted in conformance with Good Clinical Practices (GCP).

Subjects will be enrolled into the trial by documented informed consent. All subjects will be required to provide a sample of their tumor for PD-L1 immunohistochemistry (IHC) expression by central evaluation. In parallel, sites will locally assess the HPV status and the eligibility criteria. Sites will be required to submit tissue samples for PD-L1 testing; however, central pathological review for PD-L1 will not be required prior to randomization in the trial.

Once a subject is confirmed to be eligible, they will be randomized using the Interactive Voice Response System (IVRS). Once randomized, all subjects should be dosed within 3 days of the randomization date.

Approximately 780 eligible subjects will be randomized (1:1; approximately 390 subjects each), to either: pembrolizumab 200 mg Q3W (every 3 weeks) plus CRT; or placebo Q3W plus CRT (Figure 1 and Table 2).

The study will be stratified by radiotherapy (RT) regimen, tumor site/p16 status, and stage. Stratification factors are described in Section 5.6.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

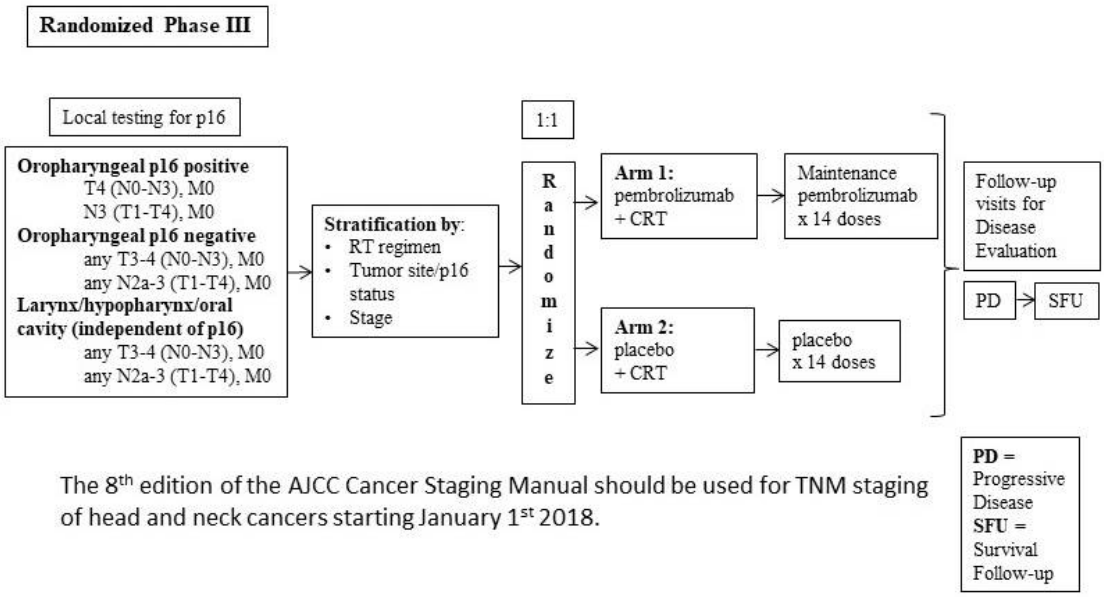
This trial will use an independent, external Data Monitoring Committee (eDMC). There will be one formal interim analysis for efficacy conducted when approximately 86% of the total number of expected event-free survival (EFS) events has been observed in the trial. See Sections 7.3.4 and 8.7 for more details about the eDMC/Interim analysis timing.

There will be one safety review by eDMC when the first 30 subjects have completed CRT. In addition to the planned interim analysis, periodic evaluations of safety data will be performed by the eDMC. If unanticipated safety issues are identified by the medical review team, the study team will request advice from the eDMC who will provide recommendations concerning the possible continuation, modification or discontinuation of the study (Section 7.3).

2.2 Trial Diagram

The trial design is depicted in Figure 1.

Figure 1 Trial Design



AJCC=American Joint Committee on Cancer; CRT=chemoradiotherapy; PD=progressive disease; RT=radiotherapy; SFU=survival follow-up.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

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

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective**: To compare event-free survival (EFS) in subjects treated with pembrolizumab in combination with CRT and subjects treated with placebo in combination with CRT.

Hypothesis: Pembrolizumab in combination with CRT is superior to placebo in combination with CRT with respect to EFS.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective:** To compare overall survival (OS) in subjects treated with pembrolizumab in combination with CRT and subjects treated with placebo in combination with CRT.

Hypothesis: Pembrolizumab in combination with CRT is superior to placebo in combination with CRT with respect to OS.

(2) **Objective:** To evaluate and compare the safety and tolerability profile of pembrolizumab in combination with CRT and subjects treated with placebo in combination with CRT.

(3) **Objective:** To compare mean change from baseline in Global health status/quality of life (QoL) and physical functioning using the EORTC QLQ-C30, and swallowing, speech and pain symptoms using the EORTC QLQ-H&N35 in subjects treated with pembrolizumab in combination with CRT and subjects treated with placebo in combination with CRT.

3.3 Exploratory Objectives

(1) **Objective**: In subjects treated with pembrolizumab in combination with CRT and subjects treated with placebo in combination with CRT, to compare:

- Local Regional Control
- Distant Metastases Free Survival
- Incidence of second Head and Neck and Other Cancers

(2) **Objective:** In subjects treated with pembrolizumab in combination with CRT and subjects treated with placebo in combination with CRT, to evaluate the relationship:

- between genetic variation and clinical outcome
- between DNA mutational burden and RNA analysis and clinical outcome

(3) **Objective:** To characterize utilities using the EuroQoL EQ-5D.

(4) **Objective:** To identify molecular (genomic, metabolic and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab in combination with CRT and other treatments.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

Pembrolizumab (previously known as MK-3475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between programmed cell death receptor (PD-1) and its ligands, programmed cell death-ligand 1 (PD-L1) and programmed cell death-ligand 2 (PD-L2).

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) 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 (Tregs) 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 [2] [3].

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 cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [4] [5].

The structure of murine PD-1 has been resolved [6]. PD-1 and its family members are Type I transmembrane glycoproteins containing an Ig-variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as 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 [5] [7] [8] [9]. 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 [10] [11]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention.

Pembrolizumab (Keytruda®) has been approved by the FDA for the treatment of melanoma, non-small cell lung cancer (NSCLC), and metastatic head and neck squamous cell carcinoma (HNSCC), and in the EU for melanoma and NSCLC. Keytruda® has been approved or is under review in many countries for the indications of melanoma, NSCLC, or Hodgkin lymphoma.

4.1.2 Pre-clinical and Clinical Trials

In cultured blood cells from healthy human donors, cancer subjects, and primates pembrolizumab strongly enhanced T-lymphocyte immune responses. It potentiated existing immune responses only in the presence of antigen and did not specifically activate T-cells.

In addition to interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), levels of other cytokines were found to be modulated by pembrolizumab.

Using an anti-murine PD-1 analog antibody, PD-1 blockade has been shown to significantly inhibit tumor growth in a variety of murine tumor models. In these experiments in mice, anti-PD-1 therapy was synergistic with chemotherapeutic agents such as gemcitabine and 5-fluorouracil (5-FU) and combination therapy resulted in increased complete tumor regression rates in vivo.

In animal studies (cynomolgus monkeys), it was demonstrated that the systemic exposure to pembrolizumab, independently of sex, increased with increasing dose. Systemic exposure for the 7-day dosing interval increased after repeated dosing from 40 to 200 mg/kg. Area under the concentration-time curve (AUC) for the 7-day dosing interval after one dose appeared to be dose-proportional from 0.3 to 200 mg/kg, suggesting dose-independent PK. Terminal half-life (t½) values from individual animals after repeated IV dosing ranged from 11.8 to 23.7 days (mean values ranged from 15.7 to 22.3 days) across the doses tested.

In cynomolgus monkeys pembrolizumab was well tolerated with systemic exposure over the course of the study and no significant in vivo toxicity was observed. In a 1-month and 6-month toxicology study, with IV pembrolizumab (up to 200 mg/kg) administered once a week and once every other week respectively, up to 200 mg/kg resulted in no adverse treatment related effects.

Additionally, in the tissue cross-reactivity study of pembrolizumab with human and monkey tissues the expected on-target staining of the membranes of mononuclear leukocytes in both species was demonstrated. Off-target cross-reactivity staining was also noted in both species but was limited to be considered related to the experimental method artifacts, i.e. tissue processing for IHC has well recognized limitations of tissue cross-reactivity studies and, thus not considered toxicologically relevant.

4.1.3 Ongoing Clinical Trials

Ongoing clinical trials are being conducted in advanced melanoma, NSCLC, a number of advanced solid tumor indications (including head and neck cancer, HNC) and hematologic malignancies. For study details please refer to the IB.

Trials evaluating pembrolizumab in head and neck cancer have demonstrated clinical activity in subjects with R/M disease. KEYNOTE-012 is a Phase 1b study of pembrolizumab in 4 indications, one of which includes subjects with human papillomavirus (HPV)-negative and HPV-positive head and neck cancer. This trial enrolled 2 HNSCC cohorts (Cohorts B and B2) for a total 192 subjects with R/M squamous cell carcinoma of the head and neck for treatment with single agent pembrolizumab.

The efficacy and safety results after long term follow-up based on pooled data from Cohorts B and B2 were presented at ASCO 2016 [12]. Among the 192 subjects with R/M HNSCC that were enrolled, 60 subjects in Cohort B were treated at 10 mg/kg every 2 weeks (Q2W) and 132 subjects in Cohort B2 were treated at 200 mg Q3W. The last subject was enrolled on 08-OCT-2014 and 32 (17%) subjects were still on treatment as of the 01-SEP-2015 data cutoff. Median age was 60 years; 83% of subjects were male; 70% had ECOG (Eastern Cooperative Oncology Group) PS (Performance Status) 1; and 61% had received ≥2 therapies for recurrent disease. ORR (confirmed) was 17.7% (95% CI, 12.6%-23.9%; 7 CRs, 27 PRs). Median follow-up duration in responders was 12.5 months (range, 8.4-24.4). As of the data cutoff, median DOR was not yet reached (range, 1.8+ to 21.8+ months) and responses were ongoing in 22 (76%) subjects. Responses of ≥6 months and ≥12 months were noted in 25 subjects and 4 subjects, respectively. Thirty-three (17%) subjects achieved stable disease. ORR was 21.9% (95% CI, 12.5%-34.0%) in HPV-positive subjects and 15.9% (95% CI, 10.0%-23.4%) in HPV-negative subjects. Median OS was 8.5 months (95% CI, 6.5-10.5), compared to the historical OS rate of 6 months for subjects who progress following first line treatment. The 6-month PFS rate was 24.9%. Treatment-related AEs (TRAEs) occurred in 122 (64%) subjects, and 23 (12%) subjects had a Grade 3-4 TRAE. No subjects died due to a TRAE. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increases were the only Grade 3-4 TRAEs observed in >2 subjects.

KEYNOTE-055 is a Phase 2 study of single agent pembrolizumab (200 mg Q3W) in subjects with R/M HNSCC who progressed following treatment with platinum and cetuximab. Preliminary results from KEYNOTE-055 were presented at ASCO 2016 [13]. A total of 172 subjects were enrolled for safety, efficacy, and biomarker analyses. Preliminary analyses focused on the first 50 subjects enrolled. Median age was 59 years; 80% of subjects were male; and 84% had ≥2 prior lines of therapy for metastatic disease. Median follow-up time at the time of the data cutoff was 6.8 months (range, 0-12.1). Thirty-five (70%) subjects experienced a TRAE, with 6 (12.0%) subjects experiencing a Grade 3-5 TRAE. Two (4%) subjects discontinued, and 1 (2%) subject died due to a TRAE. AEs of special immunologic interest occurred in 11 (22%) subjects; hypothyroidism (n = 7; all Grade 2) and pneumonitis (n = 2, Grade 2; n = 1, Grade 5) were the most common. Nine subjects had a confirmed partial response (PR) for an ORR of 18.0% (95% CI 8.6-31.4). Five subjects had ongoing responses at the data cutoff. The stable disease rate was 18.0% (n = 9; 95% CI 8.6-31.4).

Preliminary biomarker results from KEYNOTE-012 showed that when tumor and inflammatory cells were used to score PD-L1 status, an increase in ORR was observed between PD-L1+ versus PD-L1- tumors (P = 0.023); when scoring was restricted to tumor cells only, this increase was not seen. Improved PFS (P = 0.026) and OS (P = 0.008) were also observed in PD-L1+ versus PD-L1- tumors when scoring was conducted in tumor and inflammatory cells, but not tumor cells alone. In summary, inclusion of both tumor cells and inflammatory cells in IHC scoring (combined positive scoring, CPS) improves the ability to

predict response based on PD-L1 status compared to tumor cells alone (tumor proportion scoring, TPS) in subjects with R/M HNSCC. PD-L1 prevalence is unknown in locally advanced disease and is under investigation with epidemiology studies. CPS PD-L1 IHC will thus be explored as a potential biomarker in this study.

4.1.4 Rationale to Combine Pembrolizumab with Chemoradiation: Potential Activity, Treatment Sequence and Safety

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. Antibodies blocking CTLA-4 (ipilimumab) and PD-1 (pembrolizumab and nivolumab) have been approved for the treatment of advanced malignant melanoma and nivolumab has been approved for metastatic NSCLC and clear cell renal carcinoma [14] [15] [16]. Pembrolizumab has also been approved for treatment of NSCLC; in the US it is indicated for the treatment of subjects with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. In HNSCC nivolumab has been shown to improve OS in subjects who progressed within six months of platinum-based therapy [17].

Pembrolizumab was investigated in R/M HNSCC. One hundred and thirty-two subjects with advanced HNSCC irrespective of PD-L1 expression or HPV status received a fixed dose of 200 mg pembrolizumab, intravenously, Q3W. ORR was 25% (20% for the HPV-positive subgroup and 27% for the HPV-negative subgroup) [18]. Long-term responders were observed in this trial. Pembrolizumab was granted accelerated approval for subjects with R/M HNSCC with disease progression on or after platinum-containing chemotherapy by FDA on 05-AUG-2016.

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 radiotherapy. Following the report of an abscopal effect in a subject with metastatic melanoma treated with RT and ipilimumab, interest in potential synergistic treatment combining radiation and immunotherapy have emerged [19]. 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 [20] [21].

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 [22].

RT 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. RT 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 [23]. In addition, radiotherapy may augment the tumor-infiltrating lymphocytes (TILs) numbers and broaden their TCR (T-cell receptor) repertoire [24] [25] of cytotoxic

effectors cells [26]. RT also increases the expression of PD-L1 on tumor cells, which can also explain part of the synergism [27].

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 be used but the results of the current study will certainly contribute to improve our knowledge in this field.

No benefit of maintenance therapy after CRT in HNSCC has been shown so far; the only trial assessing this strategy with lapatinib has been negative [28]. Therefore, there is a huge need to identify new treatment strategies that can increase the efficacy of CRT. Preclinical studies investigating the sequence of anti-PD-1 treatment 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. This sequence is also consistent with the cetuximab/RT studies, and seems reasonable in the absence of robust data. This study will randomize high-risk locally advanced HNSCC subjects between CRT and CRT plus pembrolizumab. Pembrolizumab will be given concomitantly with CRT and continued as maintenance (total duration of pembrolizumab treatment approximately 1 year).

An initial phase IB MSD Investigator Studies Program (MSD ISP) study of pembrolizumab in combination with CRT for locally advanced HNSCC has been initiated to evaluate the safety and tolerability of pembrolizumab combined with cisplatin and RT. Treatment consists of a loading dose of pembrolizumab 200 mg IV given 7 days prior to initiation of CRT and continued every 3 weeks during CRT and following completion of CRT [29]. An interim safety analysis of the MISP study was presented at the Society for Immunotherapy of Cancer (SITC) in NOV-2016. At the time of this interim safety analysis, the study enrolled 27 subjects with 22 having completed CRT. The most commonly reported AEs (all grades) were dysphagia (21 subjects/96%) and anemia (21 subjects/96%). The most commonly reported AE Grade 3 and 4 was lymphopenia: 15 subjects/68% and 5 subjects/23%, respectively. The acute CRT-related toxicities observed are comparable to other HNSCC CRT studies. The investigators concluded combination therapy appears safe and did not significantly limit radiation (no treatment delays >5 days) or chemotherapy dosing (3 subjects with dose reductions and 6 subjects with dose omissions). Pembrolizumab discontinuation rates due to irAEs was low (1 subject discontinued due peripheral motor neuropathy [Grade 2], 1 subject discontinued due to AST increased [Grade 3]) and are comparable to monotherapy studies. No new immunologic safety signals were seen [30]. A per protocol DSMB interim efficacy analysis approved this study for continuation. The combination of pembrolizumab with CRT in this MSD ISP study supports further investigation into the potential activity and safety of this treatment regimen.

Late responders have been observed with pembrolizumab up to 1 year of treatment in the R/M setting supporting the 1-year duration of treatment with pembrolizumab. This study will be a placebo-controlled trial to avoid any bias in the comparison between the two treatment groups.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Head and neck squamous cell carcinoma (HNSCC) is the seventh most common cancer worldwide with around 600,000 new cases diagnosed per year [31]. 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. The oncogenic human papillomavirus (HPV) infection, mainly HPV-16, is an established cause of oropharyngeal cancer (tonsils and base of tongue) [33] [34]. 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.

The treatment choice depends on the location of the primary tumor, the stage of the disease, and the 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, i.e., 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 subjects with HNSCC are around 70% at 1 year and 40-60% at 5 years.

The standard of care for locally advanced stage III and IV HNSCC cancers not treated by surgery is concomitant CRT with cisplatin (level IA evidence) [35]. The updated meta-analysis of chemotherapy in combination with radiation therapy (RT) for HNSCC (MACH-NC) showed that the addition of chemotherapy concomitantly to RT improves the absolute 5-year survival by 6.5% [36]. Concomitant platinum-based CRT with high-dose-cisplatin (100 mg/m^2 day 1 & 22 & 43) is the SOC in locally advanced HNSCC. The MACH-NC meta-analysis found a greater benefit for platinum-based chemotherapy as compared with non-platinum-based CRT regimens [37]. However, the various regimens have not been directly compared with each other in adequately powered, randomized trials. Alternative cisplatin dosing schedules (e.g., 30 to 40 mg/m^2 weekly, 6 mg/m^2 daily, or 20 mg/m^2 daily for 5 days, on Weeks 1 and 5) are sometimes used for their better subject tolerance. These alternative schedules have not been directly compared to high-dose bolus cisplatin.

Cetuximab combined with RT improves locoregional control (median 24 vs. 15 months) and OS (median 49 vs. 29 months) compared to RT alone [38]. However, RT alone is no longer considered a standard approach for fit subjects with locoregionally advanced disease and how concurrent cetuximab plus RT compares with concurrent cisplatin-based CRT has so far not been adequately addressed in a randomized trial.

Combined concurrent treatment with the combination of cisplatin plus cetuximab did not appear to offer any advantages compared with concurrent cisplatin alone as reported in the randomized RTOG 0522 Phase III trial [39].

Altered (accelerated) fractionated RT improves locoregional control and OS when compared to once-daily RT as single modality treatment [40]. Accelerated RT combined with 2 courses

of high-dose cisplatin (RTOG 0129 trial) or carboplatin/5-Fluoruracil (GORTEC 99-02 trial) gave similar outcome compared to conventional CRT (7 weeks + 3 courses of chemotherapy) [41] [42]. Thus, both altered (accelerated) fractionation and standard fractionation are acceptable options.

In subjects treated with primary CRT, when residual disease in the neck is suspected 12 weeks after the end of CRT, neck dissection is recommended.

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 (40-60%). Subjects with HPV-positive oropharyngeal cancer have a better prognosis, with the exception of subjects with T4 or N3 disease for which the 5-year OS is around 50-60% (independently of their age and smoking status) [43]. This supports the development of new treatment strategies to improve the outcome of subjects' HPV-negative stage III/IV HNSCC and T4 or N3 HPV-positive oropharyngeal cancer [44].

4.2.1.1 Human Papillomavirus (HPV) and p16 expression

Expression of p16 is highly correlated to HPV in oropharyngeal cancer [45] [46] and the strong prognostic impact of p16-IHC for oropharynx cancer has been demonstrated in several clinical trials [33] [45] [47] [48]. 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 [44] [49].

The recommendations on the scoring and classification p16-IHC have been described elsewhere [50] [51] [52]. Strong and uniform p16-staining (both cytoplasmic and nuclear) in >70% of cancer cells of basaloid nonkeratinized/partially keratinized oropharyngeal carcinoma is classified as p16-positive and can be interpreted as HPV-positive [53].

Data from DAHANCA on laryngeal and hypopharyngeal SCC subjects treated with radiotherapy did not show the prognostic value of p16-positivity on the contrary to data available for oropharyngeal SCC [54]. Similar data have been presented by G. D'Souza at the 5th World Congress of the International Academy of Oral Oncology in Sao-Paulo (Brazil) in JUL-2015.

Therefore, tumors outside the oropharynx will be considered HPV-negative regardless of p16-staining results, per convention.

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Rationale for Pembrolizumab Dosage

The planned dose of pembrolizumab for this trial is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W)

- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically based pharmacokinetic [PBPK] analysis) at 200 mg Q3W

Among the eight randomized dose-comparison studies, a total of 2262 subjects were enrolled with melanoma and non-small cell lung cancer (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 three 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 head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. 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 subject covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

4.2.3.1.1 Primary

4.2.3.1.1.1 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. See Section 8.4 for the primary and secondary endpoint definitions.

Event-free survival represents a clinically significant endpoint for subjects 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. 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.

4.2.3.1.2 Key Secondary

4.2.3.1.2.1 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.

4.2.3.2 Safety

The safety objective of this trial is to evaluate the safety of pembrolizumab in combination with CRT in subjects with LA HNSCC. The primary safety analysis will be based on subjects who experienced toxicities as defined by Common Toxicity Criteria for Adverse Events (CTCAE v4.0). The severity (as CTCAE grade), attribution to drug, time-of-onset, duration, resolution and any concomitant medications administered will be recorded. Safety parameters to be analyzed include but not limited to overall AEs, SAEs, and laboratory changes.

4.2.3.3 Patient Reported Outcomes (PROs)

The EORTC QLQ-C30, EORTC QLQ-H&N35, and EuroQoL-5D (EQ-5D) patient reported outcomes (PROs) are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

The EORTC QLQ-C30, EORTC QLQ-H&N35, and EQ-5D PROs are to be completed by subjects on an electronic tablet at various time points as specified in the Trial Flow Chart, beginning with a baseline assessment at cycle 1 until year 5.

4.2.3.3.1 EORTC QLQ-C30 and EORTC QLQ-H&N35

EORTC QLQ-C30 is the most widely used cancer specific health related quality of life (QoL) instrument, which contains 30 items and measures five functional dimensions (physical, role, emotional, cognitive and social), three symptom items (fatigue, nausea/vomiting, and pain), six single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health and QoL scale [55].

The EORTC QLQ-H&N35 is in use worldwide as one of the standard instruments for measuring QoL in HNC subjects and 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) [56]. The EORTC QLQ-C30 and EORTC QLQ-H&N35 are psychometrically and clinically validated instruments appropriate for assessing QoL in subjects with HNC [56] [57]. These instruments have been widely used in Phase III trials of subjects with locoregionally advanced HNSCC receiving chemotherapy and radiation [58] [59] [60].

Clinically meaningful symptoms for HNSCC subjects have been extensively studied, and commonly identified symptoms include problems with swallowing, problems with speech, and pain in the mouth [43] [61]. 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 treatment arms is considered as clinically relevant [56] [57].

4.2.3.3.2 EQ-5D

The EQ-5D is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in health economic analyses [62]. The 5 health state dimensions in the EQ-5D include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. This trial incorporates the 5 level EQ-5D (i.e., EQ-5D-5L): each dimension is rated on a five-point scale from 1 (no problem) to 5 (unable to/extreme problems). The EQ-5D also includes a graded (0 to 100) vertical visual analog scale on which the subject rates his or her general state of health at the time of the assessment. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability [63].

4.2.3.4 Exploratory Endpoints

Potential predictive biomarkers (PD-L1, etc.) and immune dynamics (translational research) will be evaluated 1) in the subgroup of subjects with oropharyngeal p16-negative or larynx/hypopharynx/oral cavity HNC, and 2) the overall population.

4.2.3.5 Planned Exploratory Biomarker Research

Introduction: Cancer immunotherapies represent an important and novel class of anti-tumor 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 subjects. Thus, to aid future subjects, it is important to investigate the determinants of response or resistance to cancer immunotherapy as well as determinants of adverse events in the course of our clinical trials. 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, we will collect biospecimens (blood components, tumor material, etc.) to support analyses of cellular components (e.g., protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include but are not limited to:

Germline (blood) genetic analyses (e.g., SNP analyses, whole exome sequencing, whole genome sequencing): This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the subject population. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations. Finally, microsatellite instability (MSI) may be evaluated as this is an important biomarker for some cancers (i.e., 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 (i.e., 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 (MSI) may also be evaluated as this is an important biomarker for some cancers (i.e., colorectal cancer). Circulating tumor DNA and/or RNA may also be evaluated from blood samples.

Tumor and/or blood RNA analyses: Both genome-wide and targeted messenger RNA (mRNA) expression profiling and sequencing in tumor tissue and/or 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 (such as those capturing IFNγ transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated (e.g., IL-10). MicroRNA profiling may also be pursued.

Proteomics and immunohistochemistry (IHC) using blood and/or tumor: Tumor and/or blood samples from this study may undergo proteomic analyses (e.g., PD-L1 IHC). PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in subjects with NSCLC, and an IVD device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicates that this association may also be true in additional cancer types (i.e., TNBC, H&N 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, liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in subject 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.

4.2.3.6 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 subjects. 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 subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of Future Biomedical Research are presented in Section 12.2 – Collection and Management of Specimens for Future Biomedical Research.

4.3 Benefit/Risk

Subjects will receive SOC treatment or SOC treatment plus the addition of a new therapy in this clinical trial. It cannot be guaranteed that subjects in clinical trials will directly benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine. However, the SOC treatment planned for this trial has proven benefit to the LA HNSCC population.

This study will assess the safety and efficacy of pembrolizumab in combination with CRT in subjects with previously untreated, locally advanced head and neck squamous cell carcinoma. The benefit of pembrolizumab in combination with CRT in this specific subject population is unknown.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

Chemotherapy with RT is SOC for subjects with LA HNSCC. Pembrolizumab (Keytruda®) has been approved for R/M HNSCC with disease progression on or after platinum-containing chemotherapy.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male and female subjects with LA HNSCC who are at least 18 years of age will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Have a pathologically proven new diagnosis of squamous cell carcinoma of:
    a. Oropharyngeal p16 positive
        i. T4 (N0-N3), M0; or
        ii. N3 (T1-T4), M0

        OR
    b. Oropharyngeal p16 negative
        i. any T3-4 (N0-N3), M0; or
        ii. any N2a-3 (T1-T4), M0

        OR
    c. Larynx/hypopharynx/oral cavity (independent of p16)
        i. any T3-4 (N0-N3), M0; or
        ii. any N2a-3 (T1-T4), M0

        Note: Subjects with oral cavity tumors need to have unresectable disease.

    Note: Subjects with multiple synchronous tumors are not eligible for the study.
2. Be willing and able to provide documented informed consent for the trial. The subject may also provide documented informed consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
3. Have results from (local) testing of HPV status for oropharyngeal cancer defined as p16 IHC testing using CINtec® p16 Histology assay and a 70% cutoff point (please see Section 7.1.5, Tumor Tissue Collection for details). If HPV status was previously tested using this method, no additional testing is required.

    Note: 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.

    Note: HPV stratification in this trial will be performed using local testing of HPV status in subjects with oropharynx 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 may be submitted for p16 testing at the designated central laboratory.

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

4. Have provided tissue for PD-L1 biomarker analysis from a core or excisional biopsy (fine needle aspirate [FNA] is not adequate). If an excisional or incisional biopsy has been performed, subjects remain eligible for the study provided the residual disease meets the staging criteria required for the trial (eg, excisional biopsy of a lymph node with residual T4 primary). Prior surgical debulking, including tonsillectomy, for the head and neck cancer under study is not allowed.

   Note: Central pathological review for PD-L1 will not be performed before inclusion. Formalin-fixed paraffin embedded (FFPE) tumor tissue sample blocks are preferred. If submitting unstained cut slides, freshly 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 central laboratory manual).

5. Be ≥18 years of age on day of providing documented informed consent.
6. Have evaluable tumor burden (measurable and/or non-measurable tumor lesions) assessed by CT scan or MRI, based on RECIST version 1.1.
7. Be eligible for definitive CRT and not considered for primary surgery based on investigator decision.
8. Have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 performed within 10 days of treatment initiation.
9. Female subjects of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of trial treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
10. Female subjects of childbearing potential (Section 5.9.2) must be willing to use an adequate method of contraception, as outlined in Section 5.9.2 Contraception, for the course of the study through 180 days after the last dose of study medication.

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

11. Male subjects of childbearing potential (Section 5.9.2) must agree to use an adequate method of contraception, as outlined in Section 5.9.2 - Contraception, starting with the first dose of study therapy through 180 days after the last dose of study therapy.

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

12. Demonstrate adequate organ function as defined in Table 1. All screening labs should be performed within 10 days prior to treatment initiation and assessed prior to randomizing the subject. If a screening lab does not meet eligibility criteria and is repeated and assessed on Day 1 prior to randomization and the Day 1 lab meets eligibility criteria, the subject is eligible, i.e., the Day 1 lab result will be used for eligibility. 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.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1.5 x 10^9/L
Platelets	≥100 x 10^9/L
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L. Subjects are eligible if levels are reached after blood transfusion.
Renal	
Measured or calculated creatinine clearance[a] (GFR can also be used in place of CrCl)	≥60 mL/min
Calcium (corrected for albumin)	≤11.5 mg/dL or ≤2.9 mmol/L
Hepatic	
Total bilirubin[b]	≤1.5xULN or Direct bilirubin ≤ ULN for subjects with total bilirubin levels >1.5xULN
AST (SGOT) and ALT (SGPT)	≤2.5xULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5xULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT) or Partial Thromboplastin Time (PTT)[c]	≤1.5xULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

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

a. It is preferable for creatinine clearance to be calculated using the Cockcroft-Gault formula (see Appendix 12.6) but may be done per local institutional standard. The formula used to calculate creatinine clearance should be the same and consistent for all subjects at the site.

b. For subjects with Gilbert's disease, total bilirubin may be >1.5 x ULN; however, direct bilirubin must be normal.

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

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Has current participation or treatment with an investigational agent or use of an investigational device within 4 weeks of the first dose of trial treatment.
2. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor (e.g., CTLA-4, OX-40, CD137 or other immune checkpoint inhibitors) or has previously participated in MSD MK-3475 clinical trials.
3. Has received a live vaccine within 30 days prior to the first dose of study treatment.
4. Has cancer outside of the oropharynx, larynx, hypopharynx or oral cavity, such as nasopharyngeal, sinus, other para-nasal, or other unknown primary HNC.
5. Has had prior systemic therapy, targeted therapy, radiotherapy treatment or radical surgery for the head and neck cancer under study.
6. Has Grade ≥2 audiometric hearing loss. Note: Audiometric abnormalities without corresponding clinical symptoms of Grade ≥2 hearing loss will not be grounds for exclusion.
7. Has Grade ≥2 neuropathy.
8. Has Grade 3-4 bleeding due to the underlying malignancy.
9. If subject has received major surgery, and the subject has not recovered adequately from the toxicity and/or complications from the intervention prior to starting trial treatment.
10. Has known active Hepatitis B (e.g., HBsAg reactive) or C (e.g., HCV RNA [qualitative] is detected).
11. Has known history of Human Immunodeficiency Virus (HIV) (HIV-1/2 antibodies).
12. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. Corticosteroid use as pre-medication for allergic reactions (e.g., IV contrast) or as a prophylactic management of adverse events related to the chemotherapies specified in the protocol is allowed. A short course of steroids may be used as concomitant medication for either treatment of an adverse event or medical condition with Sponsor approval.
13. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
14. Has an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

15. Has history of a diagnosed and/or treated hematologic or primary solid tumor malignancy, unless in remission for at least 5 years prior to randomization. A T1-2 prostatic cancer Gleason score ≤6, superficial bladder cancer, non-melanomatous skin cancer or carcinoma in situ of the cervix is eligible. Other exceptions may be considered with Sponsor consultation.
16. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis.
17. Has had previous allogeneic tissue/solid organ transplant.
18. Has active infection requiring systemic therapy.
19. Has a history of severe hypersensitivity reaction (e.g., generalized rash/erythema, hypotension, bronchospasm, angioedema or anaphylaxis) to pembrolizumab, cisplatin or radiotherapy or their analogs.
20. Is a female subject who is pregnant or breast feeding or expecting to conceive or a male expecting to father children within the projected treatment phase of the trial, starting with the screening visit through 180 days after the last dose of trial treatment.
21. Have severe comorbidities that, in the opinion of the Investigator, might hamper participation in the study and/or the treatment administration.
22. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate in the opinion of the treating investigator.
23. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

5.2 Trial Treatment(s)

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

Country-specific differences are noted in Section 12.10.

Table 2 Trial Treatments

Arm Name	Arm Type	Intervention Name	Inter-vention Type	Dose Formu-lation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1	Experi-mental	Pembrolizumab	Biological/ Vaccine	Solution for Infusion	100 mg/ 4 mL	200 mg	IV Infusion	Day 1 of each 3-week (Q3W) cycle up to 17 doses (in Treatment 1 and Treatment 2 Phases)	Test Product	IMP	Central Sponsor
Arm 1	Experi-mental	Cisplatin	Drug	Solution for Infusion	1 mg/mL	100 mg/m^2	IV Infusion	Cycle 1, Day 8; Cycle 2, Day 8; and Cycle 3, Day 8 of Treatment 1 Phase (Cycle 3, Day 8 only applies for SFX RT regimen)	Test Product	IMP	Provided centrally by Sponsor or locally by the site
Arm 1	Experi-mental	Radiotherapy: Accelerated Fractionation (AFX) OR Standard Fractionation (SFX)	Radiation	N/A	2 Gy/ fraction	70 Gy	Accelerated Fractionation (AFX) OR Standard Fractionation (SFX)	6 weeks (35 fractions; [5 fractions on final week]) Study Weeks 2 through 7 OR 7 weeks (35 fractions) Study Weeks 2 through 8	Back-ground Treatment	NIMP/ AxMP	Provided locally by the site
Arm 2	Placebo Comparator	Placebo	Other	Solution for Infusion	N/A	N/A	IV Infusion	Day 1 of each 3-week (Q3W) cycle up to 17 doses (in Treatment 1 and Treatment 2 Phases)	Placebo	IMP	Provided locally by the site

Arm Name	Arm Type	Intervention Name	Inter-vention Type	Dose Formu-lation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm 2	Active Comparator	Cisplatin	Drug	Solution for Infusion	1 mg/mL	100 mg/m^2	IV Infusion	Cycle 1, Day 8; Cycle 2, Day 8; and Cycle 3, Day 8 of Treatment 1 Phase (Cycle 3, Day 8 only applies for SFX RT regimen)	Test Product	IMP	Provided centrally by Sponsor or locally by the site
Arm 2	Active Comparator	Radiotherapy: Accelerated Fractionation (AFX) OR Standard Fractionation (SFX)	Radiation	N/A	2 Gy/ fraction	70 Gy	Accelerated Fractionation (AFX) OR Standard Fractionation (SFX)	6 weeks (35 fractions; [5 fractions on final week]) Study Weeks 2 through 7 OR 7 weeks (35 fractions) Study Weeks 2 through 8	Back-ground Treatment	NIMP/ AxMP	Provided locally by the site

IMP=investigational medicinal product; IV=intravenous.; N/A=not applicable; NIMP/AxMP=noninvestigational/auxiliary medical product.

The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

Notes:

- A pembrolizumab or placebo priming dose will be administered one week prior to the start of CRT, followed by 2 pembrolizumab or placebo infusions during CRT, and then continued for an additional 14 doses of pembrolizumab or placebo after CRT for a total number of pembrolizumab or placebo infusions of 17 (total duration of pembrolizumab/placebo is 1 year).
- If pembrolizumab/placebo and cisplatin are delayed for reasons such as toxicity, when they are resumed, they may be administered on the same day if they were given more than 21 (±3) days since the last dose for both study medications.
- It is recommended that cisplatin start on the first day of RT (±2 days). Follow local product label and institutional guidelines (for France only: see Section 12.8). Cisplatin will not be administered after completion of RT (AFX or SFX regimen).
- If excessive toxicity with cisplatin is detected, the cisplatin dose will be changed to 40 mg/m^2 weekly (Weeks 2-8) for any new subjects enrolled into the study only upon formal notification by the Sponsor. An amendment to the protocol will be issued to incorporate the change into the trial.

Trial Treatment should begin within 3 days of the date on which the subject is randomized to start pembrolizumab/placebo priming dose. CRT should begin 1 week ±3 days after Cycle 1, Day 1. A delay in Cycle 1, Day 1 or initiation of CRT due to an adverse event is allowed. Other reasons for a delay in starting Cycle 1, Day 1 or initiation of CRT can be considered with Sponsor consultation.

All supplies indicated in Table 2 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will 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.

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of dose of pembrolizumab to be used in this trial is provided in Section 4.0 – Background & Rationale. Details on preparation and administration of pembrolizumab/placebo are provided in the Pharmacy Manual.

Preparation of cisplatin should follow the local product label (for France only: see Section 12.8). The body surface area (BSA) in m^2 should be calculated per local guidance.

5.2.1.2 Dose Modification

If appropriate, the Investigator may attribute each toxicity event to cisplatin, radiation or pembrolizumab/placebo alone and use a stepwise dose reduction according to Table 3 to Table 7.

For individual subjects 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 subject. Every effort should be made to continue RT without interruption even in the case of pembrolizumab/placebo or cisplatin toxicity. Subjects who require a 3rd dose modification to cisplatin will have that agent discontinued.

Pembrolizumab/placebo dose reductions are not permitted. Pembrolizumab/placebo 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. Subjects can have a maximum of 2 dose modifications throughout the course of the study for toxicities. If a subject experiences several toxicities and there are conflicting guidelines, please follow the most conservative dose adjustment guideline (dose reduction appropriate to the most severe toxicity).

Reduction of one systemic agent is appropriate if, in the opinion of the Investigator, the toxicity is clearly related to one of the treatments. If, in the opinion of the Investigator, the toxicity is related to the combination of more than one systemic agent, all related drugs should be interrupted/withheld and for cisplatin, adjusted according to required dose modifications.

If one or more of the study medications (i.e., pembrolizumab/placebo, cisplatin and/or radiation therapy) is discontinued, the subject may continue with the other study medications if indicated. The only exception is if radiation therapy is discontinued, cisplatin must also be discontinued.

The Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) must be used to grade the severity of adverse events. All dose modifications should be based on the AE requiring the greatest dose modification. Exceptional circumstances that may prohibit a site from following the dose modification tables below may be considered after consultation with the Sponsor.

5.2.1.2.1 Dose Modification and Toxicity Management Guidelines for Pembrolizumab

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

Dose modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (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 trial 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 are provided in Table 3.

Table 3 Dose Modification and Toxicity Management Guidelines for Immune-Related AEs 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
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	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 subjects 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). • Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Subjects 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.
	Grade 4	Permanently discontinue		

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
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	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for subjects with T1DM • Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects 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[1]		
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[1]		
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.

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
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 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs[2]	Intolerable/ persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; GI=gastrointestinal; irAE=immune-related adverse event; T1DM=Type 1 diabetes mellitus.

1. Withholding or permanently discontinuing pembrolizumab is at the discretion of the investigator or treating physician. If AE association to pembrolizumab is suspected or unknown, pembrolizumab may be interrupted and restarted if association to pembrolizumab is later ruled out.
2. Refer to Appendix 12.10.1 for France-specific guidelines for recurrent Grade 3 colitis, Stevens-Johnson Syndrome and toxic-epidermal necrolysis.

NOTE:

For subjects with Grade 3 or 4 immune-related endocrinopathy where withholding of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

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 subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., 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 subject 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 subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment	Subject may be premedicated 1.5 hrs (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., 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 subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further study drug treatment.**	No subsequent dosing
CTCAE=Common Terminology Criteria for Adverse Events; IV-intravenous; NCI=National Cancer Institute; NSAIDs=non-steroidal anti-inflammatory drugs. Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical/surgical events or logistical reasons not related to study therapy. Subjects 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 subject's study record.

5.2.1.2.2 Dose Modification and Toxicity Management for Cisplatin

Subjects can have 2 levels of dose reductions to cisplatin throughout the course of the study for toxicities as described in Table 5 and Table 6. If further toxicity occurs or the criteria for resuming treatment are not met, the subject must be discontinued from that drug and continue to participate in the study. If a subject experiences several toxicities and there are conflicting guidelines, follow the most conservative dose adjustment guideline (dose reduction appropriate to the most severe toxicity).

If excessive toxicity with cisplatin is detected, the cisplatin dose will be changed to 40 mg/m^2 weekly (Weeks 2-8) for subsequent new subjects enrolled in the study only upon formal notification by the Sponsor. An amendment to the protocol will be issued to incorporate the change into the trial. If pembrolizumab/placebo is discontinued, the subjects 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

5.2.1.2.2.1 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 creatinine clearance (CrCl). It is also associated with serum electrolyte disturbances, like hypomagnesaemia, hypocalcaemia, hypernatremia, 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.

5.2.1.2.2.2 Dose Modification and Toxicity Management Guidelines 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. If hematological toxicity has resolved, cisplatin should resume immediately per local institutional standard. If hematological toxicity has not resolved, the subject should not receive further cisplatin. The subject can continue with RT and pembrolizumab/placebo and will be followed according to study protocol. Cisplatin will not be administered after completion of RT (AFX or SFX regimen).

Permanent discontinuation of cisplatin should be considered for any severe or life-threatening event. In the event that cisplatin treatment is stopped, no substitution with, for example, carboplatin or cetuximab, will be allowed. Cessation of cisplatin therapy is not, in itself, a reason for discontinuing the subject from the study. The following dose reductions of cisplatin must be applied and carried over through all subsequent infusions (ie, no dose escalation).

5.2.1.2.2.3 Dose Reductions for Neutropenia

In the case of treatment delay due to delayed neutrophil recovery, these following policies are to be followed**:**

- 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 ≥1.0 × 10^9/L in >1 week but ≤2 weeks, proceed with a dose reduction of cisplatin.

5.2.1.2.2.4 Dose Reductions for Febrile Neutropenia

In case of any febrile neutropenia (at least CTCAE v4.0 Grade 3: absolute neutrophil count <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour), it is recommended that the subject 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.

5.2.1.2.2.5 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.

5.2.1.2.2.6 Dose Reduction for Renal Toxicity

In case of renal toxicity, the cisplatin dose must be reduced as in Table 6. Cisplatin should be dose modified based on CrCl measured within 24 hours prior to cisplatin administration.

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

5.2.1.2.2.7 Dose Reduction for Peripheral Neuropathy

A neurological examination should be performed at screening, before the second cisplatin injection and every subsequent injection per local regulations by the investigator or qualified designee. In case of symptoms or signs experienced by the subject, 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 v4.0): No change.
- Grade 2 (CTCAE v4.0): Cisplatin will be reduced to 60 mg/m^2.
- Grade ≥3 (CTCAE v4.0): Cisplatin will be discontinued.

5.2.1.2.2.8 Dose Reduction for Ototoxicity

Cisplatin is known to cause high frequency hearing loss. Follow local product label and institutional guidelines. The following dose modifications are required:

- If Grade 1 or 2 hearing loss (CTCAE v4.0) 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 v4.0) is an indication to discontinue cisplatin.

5.2.1.2.2.9 Dose Modification for Other Toxicities

If toxicity has resolved, cisplatin should resume immediately per local institutional standard. If toxicity has not resolved, the subject should not receive further cisplatin. The subject will continue with radiation treatment and will be followed-up according to the study protocol. Cisplatin will not be administered after completion of RT (AFX or SFX regimen).

Please also refer to the Multinational Association of Supportive Care in Cancer (MASCC) and European Society for Medical Oncology (ESMO) guidelines for treatment and prevention of emesis caused by highly emetic compounds [32]. 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 (DL) for Restarting Cisplatin Treatment	Discontinue Platinum
Non-hematologic	All other non-hematologic toxicities[2]	3-4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve or if >2 Dose Level reductions exceeded
	Laboratory adverse event[2]	4	Toxicity resolves to Grade 2 or less	Reduce by 1 DL	Toxicity does not resolve or if >2 Dose Level reductions exceeded

AE=adverse event; DL=dose level.

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

[2] Subjects 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, subjects with a laboratory adverse event still at Grade 2 may continue in the trial only if asymptomatic and controlled.

5.2.1.2.3 Dose Modification for Radiotherapy

All RT treatments must begin within 1 week (±3 days) after Cycle 1, Day 1 as per Trial Flow Chart (Section 6.0). Treatment interruptions are to be avoided unless medically necessary. Missed treatments should be compensated for with a twice a day (BID) treatment delivered per local SOC or continue until all 35 fractions are completed. If cisplatin and/or pembrolizumab/placebo are discontinued, subjects may stay on study treatment to complete radiation therapy.

5.2.2 Timing of Dose Administration

The dose and schedule modifications of pembrolizumab/placebo, cisplatin and radiotherapy are provided in Section 5.2.1.2 – Dose Modification.

5.2.2.1 Pembrolizumab/Placebo

Pembrolizumab or placebo will be administered as a priming dose 1 week prior to the beginning of chemoradiation (CRT (Cycle 1 Day 1 [Week 1]) followed by 2 infusions during CRT (Cycle 2 Day 1 [Week 4] and Cycle 3 Day 1 [Week 7]) and then continued for up to an additional 14 doses of pembrolizumab or placebo post-CRT for a total number of 17 pembrolizumab or placebo infusions (total duration of pembrolizumab/placebo one year).

Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. Placebo will be prepared and provided by the local unblinded pharmacist (see Pharmacy Manual), dosed and administrated in the same manner as the investigational product.

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 (i.e., infusion time is 30 minutes -5 min/+10 min).

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

5.2.2.2 Cisplatin

Cisplatin will be administered after all procedures and assessments are completed according to the Trial Flow Chart in Section 6.0.

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).

N.B. For body surface area (BSA) over 2 m^2 the cisplatin dose will be capped at the one calculated for BSA=2 m^2.

Cisplatin should start on the first day of RT (±2-day window). Before and after administration of cisplatin, adequate hydration is required and can be given as normally used in each institution. It is advised that subjects 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.

The first course of cisplatin should begin on the first day of RT (±2-day window).

Recommendations:

- Encourage the subject to drink 2-3 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:
  - 5-HT3 antagonist (e.g., granisetron 1-3 mg IV or ondansetron 8-32 mg IV or palonosetron IV 0.25 mg IV 30 minutes before cisplatin infusion).
  - aprepitant (e.g., 125 mg PO 30 minutes before cisplatin infusion and 80 mg/day PO during the 2 following days or 150 mg IV on Day 1).
  - corticosteroids (e.g., dexamethasone 20 mg once per day [12 mg once per day 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 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®) 20 mg IV should be given.
- Subjects may be weighed before and after cisplatin infusion; if weight gain, furosemide (Lasix®) could be given.
- Replace potassium (K) and magnesium (Mg) as needed.
- Check for presence of ototoxicity.

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

- Neutrophils: >1.0 × 109/L
- Platelets: >75 × 109/L
- Creatinine clearance: ≥60 mL/min (using Cockcroft-Gault formula or local institutional standard)

5.2.2.3 Radiotherapy Regimen (AFX or SFX)

The administration of RT regimen (AFX or SFX) should follow the dose parameters for either a single phase or multi-phase plan in Table 8. Intensity Modulated Radiation Therapy (IMRT) planning is required.

Table 8 RT Dose Parameters

	Single Phase IMRT (Simultaneous Integrated Boost)	**Multi-Phase Plan (Delivered with IMRT)**
Primary Site/Gross Nodes*	70 Gy in 35 fractions	70 Gy in 35 fractions (50 Gy + 20 Gy)
Regions at Microscopic Risk**	56 Gy in 35 fractions	50 Gy in 25 fractions
Intermediate Risk Areas***	63 Gy in 35 fractions	60 Gy in 30 fractions (50 Gy + 10 Gy)
* primary and nodal GTVs plus 0.5 cm to define CTV_7000 **CTV_5600 or CTV_5000 defined to include 1.0 cm expansion on all GTVs and in addition nodal regions at risk of microscopic spread according to standard anatomic guidelines relative to location and extent of gross disease *** optional volumes, defined as CTV_6300 or CTV_6000 as a 0.5 cm expansion on individual nodes thought to be at intermediate risk of involvement, such nodes will not meet criteria defined for gross involvement will be <1.5 cm in axial dimensions and in locations considered at intermediate risk such as close proximity to grossly involved nodes or primary site; other optional regions of intermediate risk would include the entire anatomic nodal level containing grossly involved nodes beyond the 70 Gy volumes defined to treat these. All PTVs defined as 0.3 to 0.5 cm expansions on CTVs based on method and frequency of Image-Guided Radiation Therapy (IGRT).		

Treatment will be delivered over 6 weeks for AFX regimen by incorporating 6 fractions per week (example: 6 doses over 5 days, 2 days off, or 6 doses over 6 days, 1 day off; 5 fractions on final week); or delivered over 7 weeks for SFX regimen by incorporating 5 fractions per week (example: 5 doses over 5 days, 2 days off).

5.2.2.3.1 Facility and Equipment

All subjects participating in the study will be treated with 6 to 10 MV photons. The preferred mode of treatment is Simultaneous Integrated Boost Intensity Modulated Radiation Therapy (SIB-IMRT) delivered by static or dynamic techniques. However, multi-phase IMRT plans

are also permitted. See Table 8 for dose parameters for SIB and multi-phase techniques. Linear accelerator or Tomotherapy based equipment is allowed.

Center credentialing will be performed according to criteria defined in the RT QA manual. Participating institutions must comply with the Radiation Therapy Quality Assurance (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.

5.2.2.3.2 Oral and Dental Check-up

See Section 7.1.2.6.

5.2.2.3.3 Subject position and data acquisition

All subjects will be irradiated in supine position. Immobilization devices such as customized masks have to be used to secure the accuracy and reproducibility of subjects positioning during RT. Preferably, mask immobilization of the head, neck and shoulders will be used. For all subjects, a planning CT 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 2-3 mm will be used. Images will be constructed with at least 512 x 512-pixel matrixes.

To enhance vascular and soft tissue contrast and to facilitate delineation of both target volumes and organs at risk (OARs), the use of intravenous contrast enhancement is strongly recommended except if medically contraindicated. If intravenous contrast is not used for the planning scan, it is mandatory the subject has either a contrast enhanced diagnostic CT and/or MRI performed no longer than 4 weeks prior to simulation. 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 quality assurance.

5.2.2.3.4 Volume definition

The definition of volumes will be in accordance with International Commission on Radiation Units & Measurements (ICRU) Reports #50, #62 and #83 [ICRU 1993; ICRU 1999; ICRU 2010]. Volumes will be named according to the target and organ at risk naming convention published by Santanam et al (2012) [64].

5.2.2.3.4.1 Delineation of the Gross Tumor Volume (GTV)

The GTV will encompass the primary tumor volume (named GTVp) and involved lymph nodes (labeled GTVn) defined with respect to physical exam and imaging studies. Involved nodes are defined as those >1.5 cm in long axis or >1cm in short (axial) axis. Nodes of any size with radiologic evidence of necrosis or extracapsular extension (ECE) are to be considered involved. Smaller nodes in close proximity to either the primary site and/or other grossly involved nodes may be considered involved. 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. FDG-PET 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.

5.2.2.3.4.2 Clinical Target Volumes (CTV)

CTVs will be defined and named according to the doses intended to be delivered. The CTV_7000 will encompass all gross tumor volume (primary and nodal) and the CTV_5600 or CTV_5000 will encompass areas beyond the CTV_7000 considered at risk of microscopic tumor involvement (beyond GTVp and GTVn including nodal levels at risk). CTVs will be defined as described below according to specific isotropic expansions, limited according to natural barriers of spread and expanded to include anatomic regions at risk of microscopic spread.

5.2.2.3.5 Clinical Target Volume at the Primary Site (CTV_7000)

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

5.2.2.3.6 Clinical Target Volume at Involved Nodes (CTV_7000)

The CTV_7000 at involved nodes will consist of a 5 mm isotropic expansion of the GTVn. The CTV_7000 should be constrained within the CTV_5600 or CTV_5000 defined to cover the microscopic/prophylactic nodal regions at risk (Table 9).

5.2.2.3.7 Clinical Target Volumes for Regions at Risk of Microscopic Tumor Involvement (CTV_5600 or CTV_5000)

The CTV_5600 or CTV_5000 will encompass:

1) A 10 mm expansion on GTVp and GTVn constrained to exclude regions protected by physical or anatomic barriers such as air (cavities or external to subject 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 [65]. In case of infiltration (or suspicion of infiltration) of the sterno-cleido-mastoid muscle, the muscle will be included in the CTV_5600 or CTV_5000.

5.2.2.3.8 Clinical Target Volumes for Regions at Intermediate Risk (CTV_6300 or CTV_6000) - Optional

An intermediate 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 abuts regions of gross tumor. See Table 9.

Radiologic anatomic boundaries of the various neck node levels are presented in Table 9 and as published by Grégoire et al [65].

Table 9 Radiologic Anatomic Boundaries of the Various Neck Node Levels

Nodal stage (AJCC 7th edition*)	Levels to be included in the CTV	
	Ipsilateral neck	Contralateral neck
N0 - N1	II-III-IV	II-III-IV
N2a – N2b	(Ib), II, III, IV, V + RP	II-III-IV
N2c	(Ib), II, III, IV, V + RP	According to N stage in contralateral neck
N3	I, II, III, IV, V + RP	According to N stage in contralateral neck
* The 8th edition of the AJCC Cancer Staging Manual should be used for TNM staging of head and neck cancers starting 01-JAN-2018.		

Peculiarities:

- Level Ib for N0: any oral cavity tumor or any primary tumor with extension to the oral cavity, e.g., to retromolar trigone, mobile tongue, inferior gum, oral side of anterior tonsillar pillar.
- Level VI: any primary site with trans- or sub-glottic extension or extension to pyriform sinus or esophagus.
- Retropharyngeal (RP): included in all cases with primary tumor extension to posterior pharyngeal wall irrespective on N stage, in such cases if primary tumor crosses midline the contralateral RP must be treated as well.
- Retrostyloid: Must be included when level II is involved. For larynx primary with N2 or greater, may treat retrostyloid node and omit RP.
- Medial Supra-clavicular fossa nodes: systematic irradiation of the supra-clavicular fossa lymph nodes in case of level IV nodal infiltration is recommended.

5.2.2.3.9 Unilateral Neck Treatment

Unilateral neck treatment is recommended for subjects with lateralized tonsilar primaries with <1cm extension into soft palate or base of tongue presenting with N0 or N1 nodal stage. Similarly, oral cavity primaries >1cm from midline and N0-N1 nodal stage may be considered for unilateral neck treatment. Unilateral treatment may be offered to subjects with N2a or N2b with <3 nodes confined to zone II as long as the primary site is lateralized as defined above. Bilateral treatment is mandatory for N2c or N3 and all laryngeal or hypopharyngeal primaries or oropharynx arising in palate, tongue base or posterior pharyngeal wall.

5.2.2.3.10 Delineation of the Planning Target Volume (PTV)

PTV_7000, PTV_6300 or PTV_6000, and PTV_5600 or PTV_5000 will be defined to enclose the corresponding CTV, respectively. Radiation dose will be prescribed, planned, and evaluated to these PTVs. PTVs are used to account for subject 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 subject 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. PTVs will also be limited in regions where they may overlap with critical organ PRVs (spinal cord and brains stem) see Table 10. In cases that do not have skin involvement with disease, the PTV does not have to extend beyond the skin surface.

5.2.2.3.11 Delineation of Organs at Risk (OAR)

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 utilizing the indicated naming convention. Guidelines for OAR contouring are provided in Table 10 and as published by Brouwer et al [66].

Table 10 Standard Organs at Risk

OAR	Standard Name
Spinal cord	SpinalCord
Brain stem	BrainStem
Lips	Lips
Oral cavity	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
Larynx (beyond PTV)	Larynx
External border of subject	External

5.2.2.3.12 Planning Organ at Risk Volume (PRV)

A 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. As such 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.

5.2.2.3.13 Dose prescription, specification and reporting in the PTV

Dose prescription, specification and reporting will be done according to ICRU report 83 recommendations.

Subjects will preferably be treated by SIB-IMRT. A median dose of 70 Gy will be prescribed to PTV_7000 in 35 fractions of 2 Gy. A median dose of 56 Gy will be prescribed to PTV_5600 in 35 fractions of 1.6 Gy. Alternately, IMRT multi-phase plans are permitted. A median dose of 50 Gy in 25 fractions to PTV_5000 followed by 20 Gy in 10 additional fractions for a total dose of 70 Gy to PTV_7000 in 2 Gy fractions. Dose-volume constraints will be used for both dose specification and dose reporting in PTV and PRV/OAR.

Treatment will be delivered over 6 weeks for AFX regimen by incorporating 6 fractions per week (example: 6 doses over 5 days, 2 days off, or 6 doses over 6 days, 1 day off; 5 fractions on final week); or delivered over 7 weeks for SFX regimen by incorporating 5 fractions per week (example: 5 doses over 5 days, 2 days off).

5.2.2.3.14 Treatment planning

Subjects will be treated by IMRT 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 really 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 below 4 mm. Dose calculations will be performed using density heterogeneity corrections.

The following dose-volume objectives (Table 11) will be used for planning, dose specification and dose reporting in PTV, PRV, and OAR:

Table 11 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_6300 or PTV_6000	≥95% of planned dose	≥90% of planned dose			63 Gy or 60 Gy ± 2%	
PTV_5600 or PTV_5000	≥95% of planned dose	≥90% of planned dose			56 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	-		-	<55Gy	-	≤44 Gy
Mandible	-		≤70 Gy		-	-
[1] D_v: Dose in v% of the volume						

5.2.2.3.15 Treatment verification and accuracy

All subjects 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 conebeam CT or tomotherapy CT images utilizing matching of bony anatomy.

5.2.2.3.16 Side effects of 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 v4.0 and will be reported in the database.

Reversible mucositis and pharyngitis is expected, and supportive care will be initiated (e.g., pain killers, 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 (e.g.,

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 subjects. Thorough dental evaluation and, if necessary, adequate care performed before the start of RT, will substantially decrease this risk.

5.2.2.3.17 Treatment Interruptions / Modifications

Radiotherapy should begin within 1 week ±3 days after Cycle 1, Day 1. Treatment interruptions are to be avoided unless medically necessary. Missed treatments should be compensated for with a BID treatment delivered. This should be limited to a maximum of twice during the 6 weeks of treatment with a minimum of 2 days between BID treatments for AFX regimen and twice during the 7 weeks of treatment with a minimum of 2 days between BID for SFX regimen. Any breaks in RT should be minimized.

5.3 Surgery Guidelines

Neck imaging (MRI or CT scan) and FDG-PET scan will be performed at 12 weeks after the end of CRT + pembrolizumab/placebo to evaluate the neck for a potential neck dissection. A neck dissection will be recommended in case of persistent disease in the neck based on a positive FDG-PET scan [25]. Neck dissection should be performed by Week 16 after the last dose of CRT but no later than Week 20 after the end of CRT and according to standard guidelines at each center.

In case of PET-positivity of the primary site, an endoscopy has to be performed within 2 weeks and a biopsy taken from the suspicious lesion. Exceptions to this may be considered with Sponsor consultation. A salvage intervention will then be performed no later than 6 weeks after the endoscopy at the discretion of the treating head and neck surgeon and Multidisciplinary Team (MDT), if the subject is found fit for the chosen intervention and accepts the intervention and its potential complications and side effects.

5.3.1 Pre-operative Assessment

Subject's Charlson co-morbidity index, ASA-score, and nutritional status are recommended pre-operatively. Also, coagulation parameters and routine labs (CBC, chemistry profile, and coagulation tests) will be performed. In case of procedures with potential long-term swallowing compromise the treating surgeon may obtain pulmonary function tests. Subjects deemed unfit for the chosen procedure will not undergo salvage. This decision will be taken individually by the treating surgeon in close collaboration with the multidisciplinary team together with the subject, assuring that the goals of quality-of-life the subject wishes to obtain are met.

Pre-operative diagnostics are comprised of a CT scan with contrast, in case of questionable soft tissue involvement an additional MRI, in case of possible bone involvement a CT scan is mandatory. An MRI of the head and neck only will suffice, if clinically bone involvement can be affirmatively excluded. An endoscopy has to be performed pre-operatively in case a salvage of the primary site is planned. In case of a negative FDG-PET scan in the primary site, but positive FDG-PET scan in the neck, a neck dissection without endoscopy suffices. A histological diagnosis at the primary site for a salvage resection is mandatory.

All results should be discussed in the MDT to determine whether or not and to what extent a subject with a positive FDG-PET scan in the neck or histologically proven disease at the primary site should be operated on.

Endoscopies in case of positive FDG-PET scans at the primary site should be performed within 2 weeks of FDG-PET result; and if positive and accepted by the MDT for surgery, should be taken for salvage intervention no later than 6 weeks after the endoscopy. A neck dissection for a FDG-PET positive neck should be done within 4 weeks from the FDG-PET result but no later than 20 weeks after the last dose of CRT.

5.3.2 Surgical Procedure Guidelines

5.3.2.1 Technique of Anesthesia

For the endoscopy a regular general anesthesia according to institutional guidelines should be performed. The same accounts for neck dissections and salvage resections with or without reconstructions.

5.3.2.2 Technique of Surgical Procedure

5.3.2.2.1 Endoscopy

The endoscopy can comprise of an examination of the oral cavity, nasopharynx, oropharynx, larynx, hypopharynx, esophagus, and tracheobronchial system (upper airways). The instruments for this examination under general anesthesia are at the discretion of the performing surgeon. A representative biopsy has to be taken from the site at which recurrence is suspected. If biopsies are returned to be inconclusive, a re-biopsy has to be performed. Exceptions to this may be considered with Sponsor consultation.

5.3.2.2.2 Neck Dissection

The neck dissection has to be at minimum a selective neck dissection comprising of the neck levels containing the suspicious nodes and in addition one adjacent level. If in other words level 3 nodes are described positive on the FDG-PET scan, a level 2, 3, 4 selective neck dissection has to be performed. In case of involvement of the sternocleidomastoid muscle, the internal jugular vein, or the spinal accessory nerve, these structures then have to be removed in addition. The surgeon should describe in his operation report the extent of macroscopic disease. Incisions and instrumentation are at the discretion of the surgeon performing the procedure.

5.3.2.2.3 Salvage Resection of the Primary Site

Salvage procedures are tailored to the location of the recurrence. The resection at each site should provide margins of at least 5 mm in the primary specimen, unless there are surgical contra-indications i.e., proximity of great vessels. The choice of procedure as well as the choice of reconstruction, if deemed necessary, is at the discretion of the surgeon.

5.3.2.2.4 Complications After Salvage Procedures And/or Neck Dissections

Complications after salvage procedures and/or neck dissections are common, and every center has certain strategies to manage them. This refers to common complications like chylous fistulas, other pharyngeal fistulas after pharyngotomies, compromise of the spinal accessory nerve, other wound healing problems, etc. In the absence of guidelines for the management of those, it will be at the discretion of the treating surgeon to manage these complications to the best of his/her knowledge.

5.3.2.3 Post-operative Care

The post-operative care is closely related to the site of intervention. In general, all efforts should be made to de-cannulate subjects with tracheostomies as fast as possible and start the subject on an oral diet. It is critical that early on in the process of swallowing and speech rehabilitation speech pathologists get involved to work on a regular basis with the subject. It is also critical to mobilize the subject as fast as his/her condition allows. These decisions need to be taken by the treating head and neck surgeon and should be individualized to the subject's ability and needs. In case of a poor swallowing rehabilitation prognosis given by the speech pathologist of the individual center, a percutaneous gastrostomy (PEG) needs to be inserted.

5.3.2.4 Pathology Specimen

Biopsies taken from the subject during an endoscopy should be kept in formalin and transported to the pathologist.

The neck dissection specimen should be sent to the pathologist level by level. In other words, in case of a selective neck dissection level 2, 3, 4, the surgeon has to send every level separately to the pathologist. It is not necessary to orient these pieces.

The primary resection specimen in case of primary site salvage has to be sent as a whole and oriented with either sutures or colors. A free margin is hereby considered to be ≥5 mm, a close margin considered to be between 1-5 mm, and a positive margin considered to be <1 mm in the primary resection specimen. If additional resections based on frozen sections are done that are considered to be part of the primary resection, these pieces have to be oriented and either sutured to the main specimen or the new true margin has to be marked through inking and the pathologist informed.

Communication from surgeon to pathologist, transport, processing (time to freezing) and reporting of the specimen should follow local practice and institutional guidelines.

Remaining tissue is required to be sent to the central laboratory (see central laboratory manual). If invasive cancer is not found at time of biopsy or surgery that was performed on study, tissue does not need to be sent to central laboratory for biomarker testing.

5.3.2.5 Evaluation 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.

5.3.2.5.1 Timing of Assessment of Complications and Mortality

Complications and mortality as a consequence of the surgical procedures will be assessed and reported as described in Sections 5.3.2 and 5.3.2.5.1. All AEs 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 to the Sponsor. All AEs meeting serious criteria considered to be post-surgical complications by the investigator from the time of protocol-specified surgery through 90 days following surgery or 30 days if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator to the Sponsor.

The reporting has to include all measures taken to manage the complication that includes operative or endoscopic interventions and all diagnostics deemed necessary.

5.3.2.5.2 Identification and grading of complications

The following tables (Table 12, Table 13, and Table 14) provide the identification and grading of post-operative complications (but not limited to):

Table 12 Endoscopy

Endoscopy:	
Dysphagia	Grade 1-3
Odynophagia	Grade 1-3
Voice changes and hoarseness	Grade 1-3
Dyspnea	Grade 1-5
Teeth damage	Grade 1-3
Esophageal perforation	Grade 4
Mediastinitis	Grade 4

Table 13 Neck Dissection

Neck Dissection:	
Bleeding	Grade 1-5
Infection	Grade 1-5
Wound healing complication	Grade 1-5
Spinal accessory nerve damage	Grade 1-3
Hypoglossal nerve damage	Grade 1-3
Vagal nerve damage	Grade 1-3
Phrenic nerve damage	Grade 1-3
Sympathetic trunk damage (Horner syndrome)	Grade 1-3
Chyle leak	Grade 1-3

Table 14 Salvage Surgery at Primary Site with or Without Reconstruction

Salvage at Primary Site with or Without Reconstruction (Free or Regional/local Flap):	
Bleeding	Grade 1-5
Infection	Grade 1-5
Fistula	Grade 1-5
Wound healing complication	Grade 1-5
Dysphagia	Grade 1-3
Odynophagia	Grade 1-3
Trismus	Grade 1-3
Loss of voice and hoarseness	Grade 1-3
Partial or total flap loss	Grade 1-5

5.4 Trial Blinding

Pembrolizumab or placebo will be prepared by the unblinded pharmacist and dispensed in a blinded fashion by an unblinded pharmacist or qualified trial site personnel. The subject, the investigator who is involved in the treatment or clinical evaluation of the subjects and the Sponsor are unaware of the group assignments. See Section 7.1.7.2 Subject Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted.

5.5 Randomization or Treatment Allocation

Randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). Subjects will be assigned randomly in a 1:1 ratio to receive either pembrolizumab or placebo in combination with chemotherapy and radiation.

RT regimen per subject will be assigned by the site through IVRS prior to randomization to ensure subjects are balanced between the arms with respect to type of RT regimen selected.

5.6 Stratification

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

1. Radiotherapy Regimen (AFX or SFX)

2. Tumor site/p16 status: 2 levels (Oropharynx – p16 positive vs. Oropharynx – p16 negative or larynx/hypopharynx/oral cavity HNSCC)
3. Stage III vs. Stage IV

5.7 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination 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 subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

5.7.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject'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 case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date should also be included on the CRF.

Supportive care is permitted for managing drug-related toxicities. See guidelines in Section 5.8. All prior/concomitant medications received within 28 days before the first dose of trial treatment through 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.7.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy;
- Immunotherapy not specified in this protocol;
- Chemotherapy not specified in this protocol;
- Radiation therapy not specified in this protocol;
- Investigational agents other than pembrolizumab/placebo.
- Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining EFS.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid

(oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g., Flu - Mist®) are live attenuated vaccines, and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an adverse event of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
    - Note: A short course of steroids may be used as concomitant medication for either treatment of an adverse event or medical condition with Sponsor approval.
    - Note: Inhaled steroids are allowed for management of asthma.
    - Note: Use of prophylactic corticosteroids to avoid allergic reactions (e.g., to IV contract dye) is permitted.
    - Note: Use of steroids for antiemetic purposes is permitted.
    - Note: Use of steroids for premedication for trial treatment is permitted.
- No prophylactic growth factor support such as erythropoietin or granulocyte-colony stimulating factor is allowed during chemoradiation treatment. An exception is that treatment of neutropenia with granulocyte-colony stimulating factor is allowed, if clinically indicated.
- 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 (BUN), and electrolytes should be monitored carefully when additional nephrotoxic agents are used. Subjects 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 subject in order to discuss renal management as well as frequency of audiometric assessments.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications that are prohibited in this trial.

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

5.8 Rescue Medications & Supportive Care

5.8.1 Supportive Care Guidelines for Pembrolizumab/Placebo

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.1.2, 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 of the event, it is determined not to be related to pembrolizumab, 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.

5.8.2 Supportive Care Guidelines for Cisplatin

See Section 5.2.2 - Timing of Dose Administration

5.8.3 Supportive Care Guidelines for Radiation

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 the CTCAE v4.0 scaling system and will be reported in the CRFs.

Reversible mucositis and pharyngitis is expected, and supportive care will be initiated (e.g., pain killers, 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 (e.g., bleeding), it may be necessary to interrupt RT for a few days. However, it is important 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 and may be managed with an NK-1 receptor antagonist such as (aprepitant, aloxi, zofran, or compazine) per local standards of care and local product label. Late effects include some degree of xerostomia and occasionally persistent dysphagia and may be managed according to local standards of care.

Mandibular osteoradionecrosis may occur in less than 5% of the subjects. A thorough dental evaluation and adequate care must be performed prior to the start of radiotherapy to substantially decrease this risk.

5.9 Diet/Activity/Other Considerations

5.9.1 Diet

Subjects 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.

5.9.2 Contraception

Pembrolizumab, cisplatin, and radiotherapy may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab, cisplatin, and radiotherapy have transient adverse effects on the composition of sperm.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they meet 1 of the following criteria:

- She is postmenopausal, defined as at least 12 months with no menses without an alternative medical cause. In women <45 years of age who are not using hormonal contraception or hormonal replacement therapy, a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- She had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening.
- She has a congenital or an acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving trial drug and for 180 days after the last dose of trial drug by complying with 1 of the following:

- Practice abstinence from heterosexual activity.

Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and European Research Councils (ERCs)/Institutional Review Boards (IRBs). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

- Use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

- Single method (1 of the following is acceptable):
  - Intrauterine device
  - Vasectomy of a female subject's male partner
  - Contraceptive rod implanted into the skin
- Combination method (requires use of 2 of the following):
  - Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
  - Cervical cap with spermicide (nulliparous women only)
  - Contraceptive sponge (nulliparous women only)
  - Male condom or female condom (cannot be used together)
  - Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Subjects should be informed that taking the trial medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the trial. In order to participate in the trial, subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of trial medication initiation (or 14 days prior to the initiation of trial medication for oral contraception) throughout the trial period up to 180 days after the last dose of trial medication. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the trial.

For countries (e.g., Germany) or sites that follow the Clinical Trial Facilitation Group guidance, please use the following:

In accordance with Clinical Trial Facilitation Group guidance, acceptable methods of contraception are those that can achieve a failure rate of less than 1% per year when used consistently and correctly and are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal

- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence

Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

Subjects 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 subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 180 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Monthly pregnancy testing is recommended per local standards if applicable.

5.9.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment on either arm of this study, the subject will immediately be discontinued from study treatment. The site will contact the subject at least monthly and document the subject'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 (e.g., 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 subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above and in Section 7.2.3.

5.9.4 Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Cisplatin has been reported to be found in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.10 Subject Withdrawal/Discontinuation Criteria

5.10.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment will still continue to participate in the trial as specified in Section 6.0 - Trial Flow Chart and Section 7.1.8.3.1 –End of Treatment Visits.

Subjects may discontinue treatment at any time for any reason or be dropped from treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from treatment by the investigator or the Sponsor if treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at treatment discontinuation are provided in Section 7.1.7 – Other Procedures.

A subject must be discontinued from treatment but continue to be monitored in the trial for any of the following reasons:

- The subject or subject's legally acceptable representative requests to discontinue treatment.
- Radiographic disease progression <u>as determined by central imaging vendor</u>

  Exception note: A subject with BICR-verified progression prior to neck dissection/salvage surgery of the primary tumor site or biopsy of the primary tumor/neck lymph nodes/metastatic site can continue with study treatment if invasive cancer is not identified based on local pathological assessment of the surgically resected or biopsied specimens.
- Salvage surgery for persistent or residual disease at the primary tumor performed for clinical progression with invasive cancer present on final pathology
- Neck dissection or surgery performed for clinical progression at any time with invasive cancer present on final pathology
- Biopsy of the primary tumor/neck lymph nodes/metastatic site positive for invasive cancer if criteria for event is fulfilled, as defined in Section 7.1.4.3
- Unacceptable adverse experiences as described in Section 5.2.1.2

- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Completed 17 doses of treatment with pembrolizumab/placebo

  Note: 17 doses of study medication (pembrolizumab/placebo) are calculated in 3-week intervals from the date of first dose.
- Administrative reasons

The End of Treatment and Follow-up Visit procedures are listed in Section 6 (Trial Flow Chart) and Section 7.1.8 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for AE monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.4.1). Subjects who discontinue for reasons other than PD/event will have post-treatment follow-up for disease status until experiencing an event/disease progression, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

Subjects who discontinue trial treatment for a reason other than either experiencing an event/disease progression or starting a new anticancer therapy will move into the Post-Treatment Efficacy Follow-Up Phase to be assessed every 3 months (91 ± 7 days) for Follow-up Years 1 through 3 and then every 6 months (± 14 days) for Follow-up Years 4 through 5 and every 6 months (± 28 days) after Year 5 after randomization according to procedures outlined in the Trial Flow Chart (see Section 6.3).

5.10.2 Withdrawal from the Trial

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

If a subject withdraws from the trial, they will no longer receive treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the trial including the procedures to be performed should a subject repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the subject, as well as specific details regarding withdrawal from Future Biomedical Research are outlined in Section 7.1.7 – Other Procedures.

5.11 Subject Replacement Strategy

A subject who discontinues from trial treatment will not be replaced.

5.12 Beginning and End of the Trial

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

For the 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.

5.13 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

The trial may be stopped early for efficacy or safety at the recommendation of the eDMC. Section 7.3.4 describes the eDMC and its responsibilities.

6.0 TRIAL FLOW CHART

6.1 Trial Screening and Treatment 1 (Pembrolizumab/Placebo + CRT)

Trial Period:	**Screening**		**Treatment 1 (3-Week Cycles) [a]**							
Visit Number/Title:	**Screening**		**Pembro / Placebo**	**Pembrolizumab / Placebo + Chemoradiation (CRT)**						
Cycle:			**Cycle 1**			**Cycle 2**			**Cycle 3**	
Week:			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Scheduled Day(s):	**-28 to -1**	**-10 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**
Scheduling Window Days (unless noted):			**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Administrative Procedures										
Informed Consent [b]	X									
Informed Consent for Future Biomedical Research (optional)	X									
Inclusion/Exclusion Criteria	X									
Subject Identification Card	X									
Demographics and Complete Medical History	X									
Disease Details	X									
Prior and Concomitant Medication Review	X		X	X	X	X	X	X	X	X [s]
Clinical Procedures/Assessments										
Review Adverse Events	X		----Continuous Reporting-----							
12-Lead Electrocardiogram (local)	X									
Full Physical Examination [c]	X									
Directed Physical Examination [c]			X	X	X	X	X	X	X	X [s]
Height [d]	X									
Weight and Vital Signs (heart rate, blood pressure, respiratory rate, temperature) [d]	X		X	X	X	X	X	X	X	X [s]
ECOG Performance Status		X[e]	X[e]	X	X	X	X	X	X	X [s]

Trial Period:	**Screening**		**Treatment 1 (3-Week Cycles) [a]**							
Visit Number/Title:	**Screening**		**Pembro / Placebo**	**Pembrolizumab / Placebo + Chemoradiation (CRT)**						
Cycle:			**Cycle 1**			**Cycle 2**			**Cycle 3**	
Week:			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Scheduled Day(s):	**-28 to -1**	**-10 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**
Scheduling Window Days (unless noted):			**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Oral and dental check-up [f]	X									
Neurological examination [g]	X						X			X [s]
Audiometric Testing [h]	X									
Fiber optic examination and endoscopy [i]	X									
Laboratory Procedures/Assessments										
Serum or Urine Pregnancy Test – if applicable [j]		X	X			X			X	
HIV/HBV/HCV serology (testing optional per site SOPs)	X									
Hematology [k]		X	X	X	X	X	X	X	X	X [s]
Comprehensive Chemistry [l]		X [l]	X	X [m]	X	X	X [m]	X	X	X [s, m]
Coagulation tests [n]		X								
Urinalysis [o]		X								
Thyroid function [p]		X								
Blood for Genetic Analysis [q]			X			X			X	
Blood for RNA Analyses [r]			X			X			X	
Blood for Plasma Biomarker Analyses [r]			X			X			X	
Blood for Serum Biomarker Analyses [r]			X			X			X	
Blood for ctDNA [r]			X			X			X	

Trial Period:	Screening		Treatment 1 (3-Week Cycles) [a]							
Visit Number/Title:	Screening		Pembro / Placebo	Pembrolizumab / Placebo + Chemoradiation (CRT)						
Cycle:			Cycle 1			Cycle 2			Cycle 3	
Week:			1	2	3	4	5	6	7	8
Scheduled Day(s):	-28 to -1	-10 to -1	1	8	15	1	8	15	1	8
Scheduling Window Days (unless noted):			+3	±3	±3	±3	±3	±3	±3	±3
Trial Treatment Administration										
Pembrolizumab/Placebo Administration [s]			X			X			X	
Cisplatin 100 mg/m^2 [s]				X			X			X [s]
Radiotherapy (AFX) [s]				X	X	X	X	X	X	
Radiotherapy (SFX) [s]				X	X	X	X	X	X	X [s]
Disease Evaluation										
CT/MRI: head-and-neck, chest, upper abdomen [t]	X									
FDG-PET or FDG-PET/CT [t]	X									
Tumor Tissue Collection										
Histology/Cytology, including p16 evaluations (p16 tested locally) [u]	X									
Tissue Collection for Biomarker Analysis (Tested Centrally) [u]	X									
Patient Reported Outcomes										
EORTC QLQ-C30 [v]			X						X	
EORTC QLQ-H&N35 [v]			X						X	
EuroQol EQ-5D [v]			X						X	

a. Treatment 1 includes pembrolizumab/placebo priming, CRT plus two pembrolizumab/placebo doses. Treatment cycles are 3 weeks (21 days). If radiation therapy is interrupted, pembrolizumab/placebo can continue to be given during radiation therapy so that it is given every 21 (±3) days. Treatment 1: Cycle 1, Day 1 treatment (pembrolizumab/placebo priming) must be given within 3 days of randomization. The window for each visit is ±3 days unless otherwise noted. The last dose of CRT is the end of treatment for Treatment 1 phase. Subjects who did not receive all pembrolizumab/placebo doses in Treatment 1 may make up these missed doses in Treatment 2 to ensure all 17 doses are administered. Pembrolizumab/placebo doses administered after CRT completion

are considered part of Treatment 2 maintenance phase. It may be necessary to perform procedures at unscheduled time points if deemed clinically necessary by the investigator. Imaging should be performed per Trial Flow Chart time points regardless of any treatment delays.

b. Documented informed consent must be obtained prior to performing any protocol-specified procedures. Results of a test performed prior to the subject providing informed consent as part of routine clinical management are acceptable in lieu of a screening test, if performed within the specified time frame.
c. Weekly Physical Examination (Full or Directed, as noted): including presence/absence of feeding tube, assessment for clinical symptoms of hearing loss and hydration status. Full physical exam and directed physical exam to be performed by the investigator or qualified designee.
d. Vital Signs to include temperature, heart rate, respiratory rate, blood pressure, and weight. Height will be measured at Screening Visit only.
e. ECOG performance status at Screening to be performed within 10 days prior to the first dose of trial treatment. ECOG performance status must be 0 or 1 on the first day of dosing.
f. Oral and dental check-up (including radiological examination) should be performed at Screening per local standards by the investigator or qualified designee. Teeth extraction, if appropriate, should be performed ideally before the locoregional imaging to avoid feeling dental artifacts. Documented routine oral and dental check-up performed within 6 weeks of trial treatment is acceptable and does not need to be repeated in Screening.
g. Neurological exam should be performed at Screening and before the second dose of cisplatin and every subsequent cisplatin injection; and at end of CRT per local standards by the investigator or qualified designee. Documented routine neurological exam performed within 6 weeks of trial treatment is acceptable and does not need to be repeated in Screening.
h. Audiometric testing will be performed at baseline and repeated during the study if hearing loss is suspected and as clinically indicated per the investigator or qualified designee. Documented routine audiometric testing performed within 6 weeks of trial treatment is acceptable and does not need to be repeated in Screening. Follow cisplatin label for ototoxicity management. Audiometry testing is required for all subjects as a screening procedure within 6 weeks prior to initiation of trial treatment.
i. A fiberoptic exam and endoscopy of the upper aerodigestive tract is required for all subjects within 8 weeks prior to randomization. Biopsies of the primary lesion(s) are also required, if appropriate. Photograph(s) of the lesion(s) and/or drawing of the finding(s) should be routinely performed to ease Gross Tumor Volume delineation according to local standards. Documented routine fiberoptic exam and endoscopy performed within 8 weeks of trial treatment is acceptable and does not need to be repeated in Screening.
j. Serum or urine pregnancy test occurs 72 hours prior to administration of trial treatment. Monthly pregnancy testing should be conducted as per local regulations where applicable.
k. Hematology: Baseline and weekly thereafter. 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. For cisplatin administration, it is best practice to obtain within 24 hours prior to cisplatin treatment. For pembrolizumab/placebo administration, it is best practice to obtain within 3 days prior to pembrolizumab/placebo treatment. See Section 7.1.3 for list of laboratory tests.
l. Comprehensive Chemistry: Baseline and weekly thereafter. 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. For cisplatin administration, it is best practice to obtain within 24 hours prior to cisplatin treatment. For pembrolizumab/placebo administration, it is best practice to obtain within 3 days prior to pembrolizumab/placebo treatment. See Section 7.1.3 for list of laboratory tests.
m. Creatinine clearance to be repeated within 24 hours prior to cisplatin treatment initiation (Treatment 1: Cycle 1, Day 8) and within 24 hours prior to start of each cisplatin administration for management of dose reduction renal toxicity guidelines.
n. Coagulation tests (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. PTT may be performed if the local lab is unable to perform aPTT. Any subject receiving anticoagulant therapy should have coagulation tests monitored closely throughout the trial. See Section 7.1.3 for list of laboratory tests.
o. Urinalysis: Baseline (within 10 days prior to the start of trial treatment). See Section 7.1.3 for list of laboratory tests.

p. TSH: In case of elevated TSH result, add Free T3 and Free T4. Free T4 should be performed on all subjects 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 lab manual for details).
q. 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 if the subject (or their legally acceptable representative) provides documented informed consent for the FBR. If the planned genetic analysis is not approved, but FBR is approved and documented informed consent is provided, this sample will be collected for the purpose of FBR.
r. Whole blood samples should be collected pre-dose. Leftover specimens will be stored for future biomedical research if the subject provides documented informed consent for future biomedical research.
s. Dosing and procedures outlined for Treatment 1: Cycle 3 Day 8 are to be followed for SFX RT regimen only. For AFX RT regimen, Treatment 1: Cycle 3, Day 8 will not be conducted, i.e., the 3rd dose of cisplatin will not be administered. If CRT administration is delayed, follow the dosing schedule and procedures in the Treatment 1 phase until CRT dosing has completed.
t. Contrast enhanced head and neck, chest and upper abdomen (to cover liver in its entirety) CT-scan, or chest CT scan plus head and neck and upper abdomen MRI, should be acquired within 6 weeks prior to randomization. The choice between CT and MRI for head and neck and upper abdominal imaging is left to the discretion of the investigator but will have to be used consistently for response evaluation, primary endpoint and follow-up unless medically contraindicated. FDG-PET or FDG-PET/CT should be acquired within 6 weeks prior to randomization. All FDG-PET reports and corresponding imaging reports (CT/MRI) obtained during screening and on-study for all randomized subjects who have completed at least one post-baseline FDG-PET scan will be collected by the Sponsor as required by the regulatory agency. Since completion of the final efficacy analysis, any additional post-baseline FDG-PET or FDG-PET/CT reports are no longer required to be collected by the Sponsor.
u. Baseline tumor tissue from a core or excisional biopsy (FNA not adequate) from subjects with oropharynx cancer must be tested locally for HPV status (if HPV status not known) prior to randomization for stratification. Baseline tumor tissue must also be provided to the central vendor for retrospective PD-L1 biomarker testing. Refer to Section 7.1.5 for additional information about tissue requirements. Detailed instructions for tissue collection, process and shipment are provided in the central laboratory manual. If the subject provides documented Future Biomedical Research (FBR) informed consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR.
v. It is a best practice and strongly recommended that PROs are administered to randomized subjects prior to drug administration, adverse event evaluation, and disease status notification. The PROs are to be completed by subjects on an electronic PRO (ePRO) tablet in the following order: EQ-5D, EORTC QLQ-C30, EORTC QLQ-H&N35. If the subject does not complete the ePROs for any reason, the Miss Mode form must be completed to capture the reason the assessment was not performed.

6.2 Treatment 2 (Pembrolizumab or Placebo Maintenance) and Post-CRT Follow-up Year 1

Trial Period:	Treatment 2 Pembrolizumab/Placebo Treatment & Post-CRT Follow-up Year 1														End of Treatment	Post-Treatment
	Treatment (3-Week Cycles)[a]															
	Pembrolizumab / Placebo Maintenance (~14 doses)															
Visit Number/Title:															**Discontinuation**	**30-Day Safety Follow up [t]**
Cycle:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		
Week:	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28**	**31**	**34**	**37**	**40**	**At time of Treatment Discontinuation or Last Dose**	**±3**
Scheduled Day(s):	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**		
Scheduling Window Days (unless noted):	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Administrative Procedures																
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Procedures/Assessments																
Review Adverse Events	----------Continuous reporting----------														X	X
Full Physical Examination [b]	X															
Directed Physical Examination [b]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight and Vital Signs (heart rate, blood pressure, respiratory rate, temperature) [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Oral and dental check-up [d]							X									
Neurological examination [e]	X															
Fiber optic examination and endoscopy [f]	X				X				X				X			
Neck Dissection (per site discretion) ± biopsy / photograph [g]				X												

Trial Period:	Treatment 2 Pembrolizumab/Placebo Treatment & Post-CRT Follow-up Year 1														End of Treatment	Post-Treatment
	Treatment (3-Week Cycles)[a]															
	Pembrolizumab / Placebo Maintenance (~14 doses)															
Visit Number/Title:															**Discontinuation**	**30-Day Safety Follow up [t]**
Cycle:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		
Week:	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28**	**31**	**34**	**37**	**40**	**At time of Treatment Discontinuation or Last Dose**	**±3**
Scheduled Day(s):	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**		
Scheduling Window Days (unless noted):	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Trial Treatment Administration																
Pembrolizumab/Placebo Administration [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Laboratory Procedures/Assessments																
Serum or Urine Pregnancy Test – if applicable [i]	X	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)	(x)		
Pulmonary Function Tests [j]			X													
Hematology [k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [t]
Comprehensive Chemistry [l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [t]
Coagulation Tests [m]	-----If Clinically Indicated-----															
Urinalysis [n]	X				X				X				X			X
Thyroid function [o]	X		X		X		X		X		X		X		X	X
Disease Evaluation																
CT/MRI: head and neck, chest and upper abdomen [p]				X					X				X			
FDG-PET or FDG-PET/CT [q]				X												
Tumor Tissue Collection																
Biopsy (optional as part of neck management)				X[r]												

Trial Period:	Treatment 2 Pembrolizumab/Placebo Treatment & Post-CRT Follow-up Year 1														End of Treatment	Post-Treatment
	Treatment (3-Week Cycles)[a]															
	Pembrolizumab / Placebo Maintenance (~14 doses)															
Visit Number/Title:															**Discontinuation**	**30-Day Safety Follow up [t]**
Cycle:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**		
Week:	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**22**	**25**	**28**	**31**	**34**	**37**	**40**	**At time of Treatment Discontinuation or Last Dose**	**±3**
Scheduled Day(s):	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**		
Scheduling Window Days (unless noted):	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Patient Reported Outcomes																
EORTC QLQ-C30 [s]	X				X				X				X		X [s]	X [s]
EORTC QLQ-H&N35 [s]	X				X				X				X		X [s]	X [s]
EuroQol EQ-5D [s]	X				X				X				X		X [s]	X [s]

a. Treatment 2 includes pembrolizumab/placebo maintenance dosing and post-CRT follow-up (Year 1) procedures. Treatment cycles are 3 weeks. The window for each visit is ±3 days unless otherwise noted. It may be necessary to perform procedures at unscheduled time points if deemed clinically necessary by the investigator. Imaging should be performed per Trial Flow Chart time points regardless of any treatment delays**.** Subjects who discontinue pembrolizumab/placebo for reasons other than an event/disease progression or starting a new anticancer therapy will move into the Post-Treatment Efficacy Follow-Up Phase (see Section 6.3 Trial Flow Chart) to be assessed every 3 months (91 ± 7 days) for Follow-up Years 1 through 3 and then every 6 months (± 14 days) for Follow-up Years 4 through 5 to monitor disease status. Imaging after 5 years should be done every 6 months (± 28 days).
b. Physical Examination (Full or Directed, as noted) – Day 1 of each Cycle: including presence/absence of feeding tube and assessment for clinical symptoms of hearing loss. Audiometric testing should be repeated during the study if hearing loss is suspected and as clinically indicated per the treating physician or qualified designee.
c. Vital Signs to include temperature, heart rate, respiratory rate, blood pressure, and weight. Height will be measured at Screening Visit only.
d. Oral/dental check-ups are recommended every 6 months throughout the trial (can be per site discretion).
e. Neurological exam should be performed as clinically indicated per local standards by investigator or qualified designee.
f. Fiberoptic exam and endoscopy of the upper-aerodigestive tract with biopsies of the primary lesion(s), if clinically indicated. Photograph(s) of the lesion(s) and/or drawing of the finding(s) should be routinely performed, if clinically indicated.
g. Neck Dissection: See Section 7.1.2.10 for Algorithm (Figure 2). Can be performed approximately 16-20 weeks post-CRT.
h. Pembrolizumab / placebo may be dosed in total for up to 17 doses.
i. Serum or urine pregnancy test occurs within 72 hours prior to administration of trial treatment. (x) = Monthly pregnancy testing is optional unless required per local regulations where applicable.
j. Pulmonary Function Tests may be checked as part of pre-operative procedures for Post-CRT Neck Evaluation, if indicated.

k. Hematology: Every cycle (e.g., Day 1 of each 3-week cycle) prior to pembrolizumab/placebo treatment and as clinically indicated during the remainder of the Year 1 follow-up visits. See Section 7.1.3 for list of laboratory tests.
l. Comprehensive Chemistry: Every cycle (e.g., Day 1 of each 3-week cycle) prior to pembrolizumab/placebo treatment and as clinically indicated during the remainder of the Year 1 follow-up visits. See Section 7.1.3 for list of laboratory tests.
m. Any subject receiving anticoagulant therapy should have coagulation tests monitored closely throughout the trial. PTT may be performed if the local lab is unable to perform aPTT. Coagulation tests (PT/INR and aPTT) may be checked as part of pre-operative procedures for Post-CRT Neck Evaluation, if indicated.
n. Urinalysis: specific gravity, pH, proteins, glucose, blood using a dipstick; elements and microscopic examination if needed. See Section 7.1.3 for details.
o. TSH: in case of elevated TSH add Free T3 and Free T4.
p. Contrast enhanced head and neck, chest and upper abdomen (to cover liver in its entirety) CT-scan, or chest CT scan plus head and neck and upper abdomen MRI, (use the same modality as screening unless medically contraindicated). The examination should be performed at 12 weeks (± 7 days) ***after*** the end (last dose) of CRT, then every 3 months (± 7 days) during Years 1-3 after randomization; then every 6 months (± 14 days) during Years 4-5 and every 6 months (±28 days) after Year 5.
q. FDG-PET or FDG-PET/CT scan should be performed at 12 weeks (± 7 days) ***after*** the last dose of CRT. The neck dissection could be performed at approximately 16-20 weeks after the end of CRT, if indicated. All FDG-PET reports and corresponding imaging reports (CT/MRI) obtained during screening and on-study for all randomized subjects who have completed at least one post-baseline FDG-PET scan will be collected by the Sponsor as required by the regulatory agency. Since completion of the final efficacy analysis, any additional post-baseline FDG-PET or FDG-PET/CT reports are no longer required to be collected by the Sponsor.
r. Tumor tissue collection for diagnostic purposes and biomarker analysis should be timed with the neck dissection procedure. Remaining tissue is required to be sent to the central laboratory (see central laboratory manual). If invasive cancer is not found at time of biopsy or surgery that was performed on study, tissue does not need to be sent to central laboratory for biomarker testing.
s. It is a best practice and strongly recommended that PROs are administered to randomized subjects prior to drug administration, adverse event evaluation, and disease status notification. The PROs are to be completed by subjects on an electronic PRO (ePRO) tablet in the following order: EQ-5D, EORTC QLQ-C30, EORTC QLQ-H&N35. If the subject does not complete the ePROs for any reason, the Miss Mode form must be completed to capture the reason the assessment was not performed.
t. A subject may discontinue from trial treatment for a reason other than experiencing an event/disease progression or starting a new anticancer therapy but will remain in the trial for post-treatment follow-up to monitor disease progression as outlined in Section 7, as long as the subject does not withdraw consent. Unresolved abnormal lab results associated with drug-related AEs should be followed until resolution.

6.3 Post-Treatment Efficacy Follow-up Visits

Trial Period:	**Post-Treatment Follow-up Visits [a]**							
Visit Title:	**Follow up 1**	**Follow up 2**		**Follow up 3**		**Follow up 4**		**After 5 years**
Time Period:	**Year 2[c]**	**Year 3**		**Year 4**		**Year 5**		
Scheduled Interval:	**Q3M**	**Q3M**	**Q12M**	**Q6M**	**Q12M**	**Q6M**	**Q12M**	**Q6M**
Scheduling Window Days (unless noted):	**±7**	**±7**	**±14**	**±14**	**±14**	**±14**	**±14**	**±28**
Administrative Procedures								
Prior and Concomitant Medication Review	----If Clinically Indicated------							
Post-study Anticancer Therapy Status	X	X		X		X		X
Survival Status [b]	←----------→							
Clinical Procedures/Assessments								
Review Adverse Events [d]	----------Continuous reporting----------							
Directed Physical Examination [e]	X	X		X		X		
Weight and Vital Signs (heart rate, blood pressure, respiratory rate, temperature) [f]	X	X		X		X		
Oral and dental check-up [g]		X		X		X		
ECOG Performance Status	X	X		X		X		
Fiber optic examination and endoscopy	----If Clinically Indicated------							
Tumor Biopsy [h]	----If Clinically Indicated------							
Laboratory Procedures/Assessments								
Hematology [i]	----If Clinically Indicated------							
Comprehensive Chemistry [j]	----If Clinically Indicated------							

Trial Period:	**Post-Treatment Follow-up Visits [a]**							
Visit Title:	**Follow up 1**	**Follow up 2**		**Follow up 3**		**Follow up 4**		**After 5 years**
Time Period:	**Year 2[c]**	**Year 3**		**Year 4**		**Year 5**		
Scheduled Interval:	**Q3M**	**Q3M**	**Q12M**	**Q6M**	**Q12M**	**Q6M**	**Q12M**	**Q6M**
Scheduling Window Days (unless noted):	**±7**	**±7**	**±14**	**±14**	**±14**	**±14**	**±14**	**±28**
Coagulation tests	----If Clinically Indicated------							
Urinalysis [k]	----If Clinically Indicated------							
Thyroid function	X	----If Clinically Indicated------						
Disease Evaluation								
CT/MRI: head-and-neck, chest and upper abdomen [l]	X	X[l]		X		X		X
Patient Reported Outcomes								
EORTC QLQ-C30 [m]	X		X		X		X	
EORTC QLQ-H&N35 [m]	X		X		X		X	
EuroQol EQ-5D [m]	X		X		X		X	

a. It may be necessary to perform procedures at unscheduled time points if deemed clinically necessary by the investigator. Imaging should be performed per Trial Flow Chart time points regardless of any treatment delays. All visit procedures/assessments should be done every 3 months (i.e., at Months 3, 6, 9 and 12) during Follow up 1 and 2, and every 6 months (i.e., at Months 6 and 12) during Follow up 3 ,4 and thereafter , and the assessments listed under Q12M should be done at Month 12 only of each year. *Note:* The post-treatment assessments and imaging schedule start time begins on the last day of CRT. The timeframe for the Post-Treatment Follow-up phase (Follow-up 1 through 4 and thereafter) begins at randomization. The imaging visit schedule is the same as the post-treatment follow-up visit schedule.

b. Survival status will be collected during the post-treatment follow-up visits. Subjects who do not/will not have a scheduled study visit during the Sponsor-defined time period will be contacted by telephone or have their medical records reviewed for their survival status (excluding subjects that have had a death event previously recorded). After 5 years, subjects will be followed by telephone to monitor survival and anticancer treatment status every 6 months (± 28 days), until consent withdrawal from trial, becoming lost to follow-up, death or end of the study, whichever is earlier. The Sponsor may request survival status to be assessed at additional time points during the course of the study. At the time of obtaining survival status, evidence of an event/progression confirmed by biopsy and/or surgery (e.g., biopsy and/or surgery reports) will also be collected for subjects in survival follow-up who have not yet experienced an event/progression, if available, and maintained in source documentation and recorded in the database, as appropriate. Additionally, imaging assessment performed as a part of standard of care to evaluate disease status for subjects 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 database.

c. For subjects who discontinue study treatment early, the remainder of their post-treatment follow-up for the 1st year should be completed as specified in Follow-up 1. These subjects should remain in Follow-up 1 for up to a total of 2 years.
d. Treatment-related late toxicity meeting serious criteria may be collected for up to 5 years.
e. Physical Examination (Directed) to include ECOG and may include presence/absence of feeding tube, gastrostomy or tracheostomy positioning and assessment for clinical symptoms of hearing loss. Audiometric testing should be repeated during the study if hearing loss is suspected and as clinically indicated per the treating physician or qualified designee.
f. Vital Signs to include temperature, heart rate, blood pressure, respiratory rate, and weight.
g. Oral/dental check-ups are recommended every 6 months throughout the follow-up visits (or as per site discretion).
h. Remaining tissue should be sent to the central laboratory (see central laboratory manual) if invasive cancer is found at time of biopsy.
i. Hematology: if clinically indicated. See Section 7.1.3 for list of laboratory tests.
j. Comprehensive Chemistry: If clinically indicated. See Section 7.1.3 for list of laboratory tests.
k. If clinically indicated. Urinalysis: specific gravity, pH, proteins, glucose, blood using a dipstick; elements and microscopic examination if needed. See Section 7.1.3 for details.
l. Contrast enhanced head and neck, chest and upper abdomen CT-scan, or chest CT scan plus head and neck and upper abdomen MRI, (use the same modality as screening unless medically contraindicated). The examination should be similar to the one performed during the work-up procedure: every 3 months (± 7 days; 3 months = 91 days) during Years 1-3 after randomization; then every 6 months (± 14 days) up to and including Year 5 and every 6 months (± 28 days) after Year 5 after randomization. All FDG-PET (if acquired) reports and corresponding imaging reports (CT/MRI) obtained during screening and on-study for all randomized subjects who have completed at least one post-baseline FDG-PET scan will be collected by the Sponsor as required by the regulatory agency. Since completion of the final efficacy analysis, any additional post-baseline FDG-PET or FDG-PET/CT reports are no longer required to be collected by the Sponsor.
m. It is a best practice and strongly recommended that PROs are administered to randomized subjects prior to AE evaluation, and disease status notification. The PROs are to be completed by subjects on an electronic PRO (ePRO) tablet in the following order: EQ-5D, EORTC QLQ-C30, EORTC QLQ-H&N35. If the subject does not complete the ePROs for any reason, the Miss Mode form must be completed to capture the reason the assessment was not performed. Since completion of the final efficacy analysis, any additional ePROs are no longer required to be collected by the Sponsor.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, 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.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented informed consent from each potential subject (or their legally acceptable representative) prior to participating in this clinical trial or Future Biomedical Research. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate documented informed consent is in place.

7.1.1.1.1 General Informed Consent

Informed consent given by the subject or their legally acceptable representative must be documented on a consent form. The form must include the trial protocol number, trial protocol title, dated signature, and /agreement of the subject (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 subject (or their legally acceptable representative) before participation in the study.

The initial informed consent, any subsequent revised informed consent, and any written information provided to the subject must receive the IRB/IEC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. 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 subject's or the subject's legally acceptable representative's dated signature.

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

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, or the subject'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 subject before performing any procedure related to future biomedical research.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. 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 subject with a Subject Identification Card immediately after the subject provides documented informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

Demographics and a complete medical history will be obtained by the investigator or qualified designee. The medical history will consist of age, smoking and alcohol habits, use of recreational drugs, concurrent illnesses, use of adequate contraception, history of past oncological or chronic diseases, assessment of symptoms suggestive of peripheral neuropathy and weight loss.

7.1.1.5 Disease Details

The investigator or qualified designee will obtain prior and current details regarding the subject’s HNC.

7.1.1.6 Prior and Concomitant Medications Review

7.1.1.6.1 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 subject within 28 days before the first dose of trial treatment. Prior treatment for other cancers will also be recorded as a prior medication.

7.1.1.6.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial.

7.1.1.7 Post-study Anticancer Therapy Status

Investigator or qualified designee will record anticancer therapy medication, if any, taken by the subject after discontinuing from trial treatment.

7.1.1.8 Survival Status

Once a subject experiences an event/disease progression, the survival status will be collected during the follow-up visits for the first five years and thereafter to assess for survival status until death, withdrawal of consent, or at the end of the study, whichever occurs first. Survival status could be collected by telephone.

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an eDMC review, interim and/or final analysis. Upon Sponsor notification, all subjects 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 subjects that have a previously recorded death event in the collection tool). At the time of obtaining survival status, evidence of an event/progression confirmed by biopsy and/or surgery (e.g., biopsy and surgery pathology reports) will also be collected for subjects in survival follow-up who have not yet experienced an event/progression, if available, and maintained in source documentation and recorded in the database, as appropriate. Additionally, imaging assessment performed as a part of standard of care to evaluate for disease status for subjects 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 database.

7.1.1.9 Assignment of Screening Number

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

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

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.8.1.

7.1.1.10 Assignment of Treatment/Randomization Number

All eligible subjects will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures

occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

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

7.1.1.11 Trial Compliance (Medication/Diet/Activity/Other)

Interruptions from the protocol-specified treatment plan due to medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, subject vacation, and/or holidays) >6 weeks between pembrolizumab/placebo doses and/or >12 weeks between pembrolizumab/placebo doses for drug-related adverse events associated with pembrolizumab exposure (see Section 5.2.1.2.1 for dose modification guidelines for drug-related events) require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Subjects may receive up to 17 doses of pembrolizumab/placebo. If an interruption occurs, the subject should restart pembrolizumab/placebo as soon as medically appropriate with the subsequent cycle and should not skip cycles. The subject, after an interruption, may restart pembrolizumab/placebo cycles as a monotherapy without delay from the original 3-week interval schedule, but all future doses should be recalculated in 3-week intervals. Subjects should be administered all planned 17 cycles, which could extend beyond the 1-year timeframe of the study in order to be considered as having completed study treatment. A subject may, if medically appropriate, stop treatment at the end of 1 year.

Administration of trial medication will be monitored by the investigator and/or institution staff. The total volume of pembrolizumab/placebo infused will be compared to the total volume prepared to determine compliance with each dose of pembrolizumab/placebo administered.

The instructions for preparing and administering pembrolizumab/placebo are provided in the Pharmacy Manual. Treatment with standard therapies will be prepared and administered as per the approved product label.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event Monitoring

All adverse events (AEs) will be recorded; the investigator or qualified designee will assess whether those events are drug-related (reasonable possibility, no reasonable possibility) and this assessment will be recorded in the database for all AEs. Adverse events will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE v4.0. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment. The collection period will begin during registration. All AEs must be followed until resolution or stabilization.

Hematological and biochemistry AEs will be assessed on the basis of regular blood counts. The nadir count will be computed at each study medication administration and graded according to the CTCAE v4.0 (see Section 7.2.4). Non-hematological acute side effects will be assessed and reported separately for each study medication administration and graded

according to the CTCAE v4.0. Post-treatment treatment-related late toxicity meeting serious criteria will be recorded as well up to 5 years.

Refer to Section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 12-Lead ECG

A standard 12-lead 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.

7.1.2.3 Physical Examination

7.1.2.3.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination during the screening period. Clinically significant abnormal findings should be recorded as medical history. Additional full physical exams should be performed as specified in the Trial Flow Chart. After the first dose of trial treatment, new clinically significant abnormal findings should be recorded as AEs.

The physical examination at Screening will include height, weight and assessment of presence or absence of a feeding tube. During CRT, weekly physical examinations will consist of weight according to standard practice, evaluation for the signs of dehydration, and evaluation for the need for feeding tube, audiometry and hydration.

During the post-treatment follow-up visits for disease evaluation, physical examinations will be performed at each visit.

7.1.2.3.2 Directed Physical Examination

For cycles that do not require a full physical examination per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical examination as clinically indicated prior to dosing on Day 1 of each treatment cycle or other specified time point in the Trial Flow Chart – Section 6.0. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.4 Height, Weight and Vital Signs

Vital signs include weight, heart rate, blood pressure (diastolic and systolic blood pressures), respiratory rate and temperature. Vital signs will be measured at Screening and weekly during CRT (prior to the start of the cisplatin infusion on the day of chemotherapy administration) and on Day 1 of each cycle during pembrolizumab/placebo maintenance, and at each post-treatment follow up visit.

Height will be measured at Screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator or qualified designee will assess ECOG performance status (See Section 12.5) at Screening, prior to dosing during each treatment cycle and during regular Follow-up visits.

7.1.2.6 Oral and Dental Check-up

All subjects 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 CRT should be as long as possible to permit healing and subject comfort prior to the commencement of treatment. If more than 2 teeth are to be extracted, this should be done prior to CT simulation. Oral/dental check-ups are recommended every 6 months throughout the trial (can be per site discretion). Adequate dental care (including daily fluorine application) should be recommended as an option to all subjects, at least during follow-up. Documented routine oral and dental check-up performed within 6 weeks of trial treatment is acceptable and does not need to be repeated in Screening.

7.1.2.7 Neurological Examination

A neurological examination must be performed at Screening, before the second cisplatin injection, and every subsequent injection per local standards by the investigator or qualified designee. In case of symptoms or signs experienced by the subject, more frequent examinations should be performed per local standards by the investigator or qualified designee and the following dose modification (see Section 5.2.1.2.2.7). Documented routine neurological exam performed within 6 weeks of trial treatment is acceptable and does not need to be repeated in Screening.

7.1.2.8 Audiometric Testing

Audiometric assessments should be performed by a qualified audiologist, investigator, or qualified designee for all subjects at Screening (within 6 weeks prior to randomization). The procedure used for the audiometric exam should be conducted in accordance with local institutional practice. As part of the screening assessment, the audiologist, Investigator or qualified designee will assess hearing aid use prior to the start of study treatment. If auditory symptoms develop after the screening assessment and prior to treatment initiation, the audiometric assessments should be repeated prior to treatment initiation. Additional comprehensive audiometric assessments should be conducted as deemed appropriate by the audiologist, Investigator, or qualified designee and following local cisplatin product label (For France only: see Section 12.8) to provide continued safety assessment (see also, Section 6.0 Study Flow Chart). Documented routine audiometric testing performed within 6 weeks of trial treatment is acceptable and does not need to be repeated in Screening.

7.1.2.9 Fiberoptic Examination and Endoscopy

Fiberoptic examination and endoscopy will be performed (under general anesthesia, as appropriate) of the upper-aerodigestive tract.

An endoscopy/fiberoptic exam is required during Screening for all subjects within 8 weeks prior to the initiation of trial treatment. Documented routine fiberoptic exam and endoscopy performed within 8 weeks of initiation of trial treatment is acceptable and does not need to be repeated during the 28-day screening period.

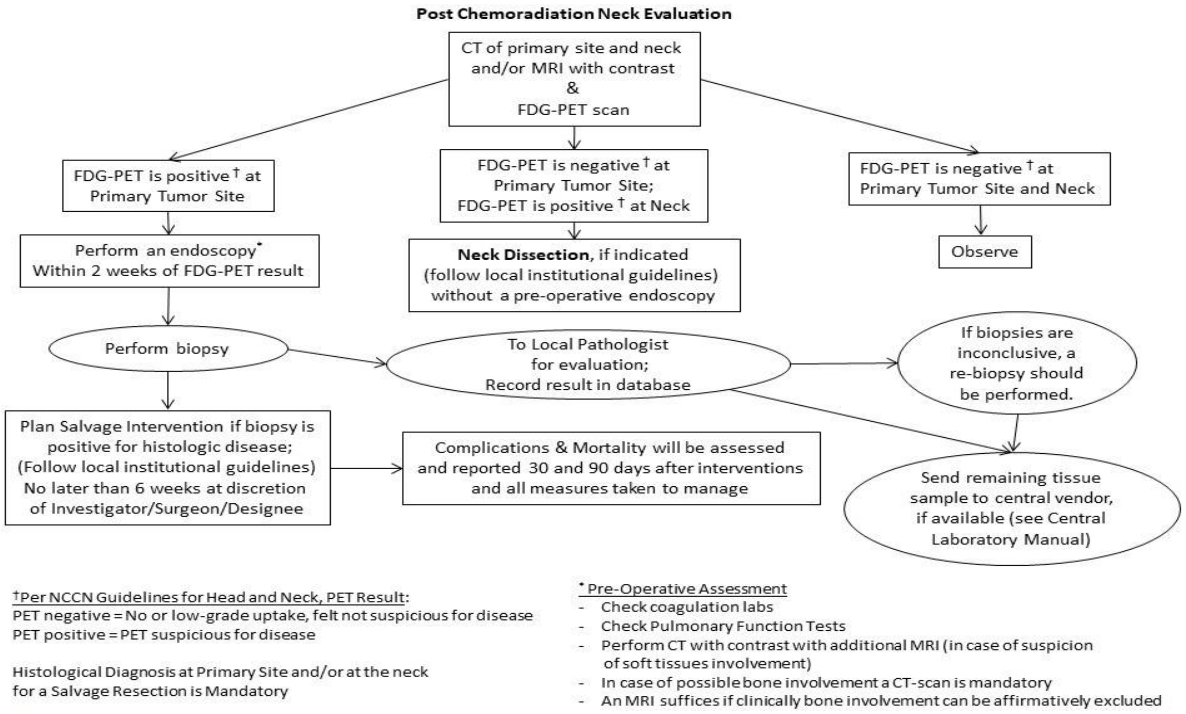
Following randomization, as stated in Section 5.3 and as per Figure 2, an endoscopy/fiberoptic exam is also required between 12-14 weeks after completion of CRT for subjects whose primary tumor site is positive on FDG-PET scan and suspicious for residual disease. Fiberoptic examination and endoscopy can also be performed (under general anesthesia, as appropriate) of the upper-aerodigestive tract if clinically indicated per the Trial Flow Chart.

Photographs of the lesion(s) and/or drawing of the finding(s) should be routinely performed to ease Gross Tumor Volume delineation, if clinically indicated.

7.1.2.10 Neck Dissection (if Clinically Indicated)

Neck imaging (see Section 7.1.4) will be performed per the Trial Flow Chart (see Section 6.0) to evaluate the neck for a potential neck dissection. A neck dissection will be recommended in case of persistent disease in the neck post CRT based on the results of the FDG-PET or FDG-PET/CT scan. If clinically indicated, neck dissection must be performed before 20 weeks after the end of CRT and according to standard guidelines at each center. During the procedure, pembrolizumab/placebo should be held.

Figure 2 Post-Chemoradiation Neck Evaluation



1. Note: Complications and mortality should be assessed after Neck Dissection and Salvage Surgery according to Section 5.3.2.5.1.
2. Exceptions to completing biopsy may be considered with sponsor consultation (see Section 5.3).

7.1.3 Laboratory Procedures/Assessments

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

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 subject 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 subjects.

7.1.3.1 Serum or Urine Pregnancy Test

Serum or urine pregnancy test occurs within 72 hours prior to administration of trial treatment. Monthly pregnancy testing should be conducted as per local regulations where applicable.

7.1.3.2 Pulmonary Function Test

Pulmonary function tests may be performed pre-operatively for neck management per local institutional practice and as clinically indicated thereafter.

7.1.3.3 HIV, HBV, HCV Serology

HIV, HBV, and HCV serology will be conducted on subjects 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 quantitative HCV RNA results greater than the lower limits of detection of the assay.

7.1.3.4 Laboratory Safety Evaluations (Hematology, Chemistry, Coagulation and Urinalysis)

Laboratory tests for hematology, chemistry, coagulation, and urinalysis are specified in Table 15. All laboratory tests to determine eligibility and Drug-Induced Liver Injury (DILI) (see Sections 5.1 Entry Criteria Table 1 and 7.2.4.2 Events of Clinical Interest, respectively), creatinine clearance prior to cisplatin dosing, creatinine and thyroid testing as specified in footnote b are mandatory; all other laboratory tests are recommended and may be performed according to your local institutional standard.

Table 15 Laboratory Tests

Hematology	Serum Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood (dipstick)	
Hemoglobin	Alkaline phosphatase	Glucose	Serum human chorionic gonadotropin (hCG)[a]
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT [f]
RBC count	A measure of carbon dioxide (CO_2 or bicarbonate) [d]	pH	Hepatitis [h]
Absolute Neutrophil Count (ANC)	Calcium [c]	Microscopic exam, as needed	HIV
Absolute Lymphocyte Counts / Lymphocytes	Chloride		
	Creatinine		
	Creatinine clearance [g]		FT3 [b]
	GGT [h]		FT4 [b]
	Glucose		TSH
	Magnesium		HBV, HCV
	Phosphorus		
	Potassium		
	Sodium		
	Direct Bilirubin[i]		
	Total Bilirubin		
	Total protein		
	Blood Urea Nitrogen (BUN) [e]		
	Uric Acid [h]		
	Urea [e]		
	LDH [h]		

Hematology	Serum Chemistry	Urinalysis	Other

ALT=alanine aminotransferase, ANC=absolute neutrophil count, aPTT= activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CO_2=carbon dioxide, CrCL=creatinine clearance, FT3=free triiodothyronine, FT4=free thyroxine, GGT=gamma glutamyl transferase, HBV=hepatitis B virus, hCG=human chorionic gonadotropin, HCV=hepatitis C virus, HIV=human immunodeficiency virus, INR=international normalized ratio, LDH=lactate dehydrogenase; PT=prothrombin time, RBC=red blood cell, TSH=thyroid stimulating hormone, WBC=white blood cell.

a During the concomitant chemo-radio-immunotherapy treatment phase and the pembrolizumab/placebo maintenance phase, monthly pregnancy testing should occur within 72 hours prior to administration of trial treatment and be conducted as per local regulations where applicable.

b In case of elevated TSH result, add Free T3 and Free T4. Free T4 should be performed on all subjects 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 lab manual for details).

c. Corrected calcium should be checked for subjects with hypoalbuminemia.

d If available as standard of care in your region. The carbon dioxide may be either a measurement of CO2 or bicarbonate as an electrolyte.

e Blood Urea Nitrogen is preferred; if not available urea may be tested.

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

g CrCl during screening is required within 10 days prior to treatment initiation and should be assessed prior to randomization. It does not need to be repeated within 24 hours prior to treatment initiation (Treatment 1: Cycle 1, Day 1), unless clinically indicated. CrCl must be repeated within 24 hours prior to start of each cisplatin administration for management of dose reduction for renal toxicity guidelines.

h Only if clinically indicated

i Only if total bilirubin is elevated above the upper limit of normal

7.1.3.5 Pharmacokinetic Evaluations

The accumulation of robust PK and ADA data has allowed for the adequate characterization the clinical pharmacology of pembrolizumab across indications. Therefore, upon approval of Amendment 04 each site is to stop the collection of PK and ADA samples for all subjects. Blood samples for PK and ADA collected prior to Amendment 04 may be stored. Analysis will be performed only if required.

7.1.3.6 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the central laboratory manual.

7.1.3.7 Future Biomedical Research Samples

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

7.1.4 Disease Evaluation

7.1.4.1 CT/MRI: Head and Neck, Chest and Upper Abdomen

During screening, contrast enhanced head and neck, chest and upper abdomen CT scan or chest CT scan plus head and neck and upper abdomen MRI should be acquired within 6 weeks of randomization. The choice between CT and MRI for head and neck imaging is left to the discretion of the investigator but will have to be used consistently for response evaluation, primary endpoint and follow-up. The upper abdomen imaging anatomy should cover the liver in its entirety.

The follow-up imaging should be acquired at Week 12 post-CRT and then every 3 months (91 ± 7 days) for three years after randomization, then every 6 months (±14 days) for Years 4 through 5. Imaging after 5 years should be done every 6 months (±28 days). For all imaging, the clock will start at the end of CRT (i.e., last dose of CRT). All of these visits should stay on track using the last dose of CRT as the starting clock, i.e., if one of the imaging visits is late (even Week 12), the subject will stay on the original schedule starting with the last dose of CRT for all future visits; do not recalculate.

The same modality used at screening should be used during pembrolizumab maintenance or placebo treatment and during the post-treatment follow-up visits as described in Section 6.0. If there is a medical contraindication to using the same modality, a different imaging modality may be used.

7.1.4.2 FDG-PET

During screening, an FDG-PET or FDG-PET/CT scan should be acquired within 6 weeks of randomization. Then, at 12 weeks post-CRT ±1 week (approximately Week 19 or Week 20) an FDG-PET or FDG-PET/CT scan should be acquired as part of neck management (see Figure 2, See Section 7.1.2.10). The timing of the FDG-PET or FDG-PET/CT scan should be such that the neck dissection could be performed approximately 16-20 weeks post-CRT, if indicated.

The FDG-PET/CT may replace the CT/MRI scan if the CT is of diagnostic quality when this is the local standard practice.

All FDG-PET or FDG-PET/CT and corresponding CT/MRI imaging reports obtained during screening and on-study for all randomized subjects who have completed at least one post-baseline FDG-PET or FDG-PET/CT scan will be collected by the Sponsor as required by the regulatory agency. Since completion of the final efficacy analysis, any additional post-baseline FDG-PET or FDG-PET/CT reports are no longer required to be collected by the Sponsor.

7.1.4.3 Assessment for Residual Disease and/or Disease Progression

The assessment of residual disease and/or disease progression of a subject based on radiographic progression per RECIST 1.1 by BICR as well as local pathological evaluation of disease, as indicated, is described below and in Table 16.

Criteria for events of the primary tumor site:

The management of the primary tumor site will be based on investigator-assessed response seen on FDG-PET/CT scan 12 weeks after completion of CRT, as illustrated in Figure 2. As per Section 8.4.1.1, salvage surgery of the primary tumor site completed at any time with invasive cancer present meets criteria for local treatment failure and is an event.

A biopsy confirming the presence of residual invasive cancer in the primary tumor site completed <12 weeks after completion of CRT is only an event if there is also radiographic progression per RECIST 1.1 by BICR.

If more than 12 weeks after completion of CRT, salvage surgery is indicated but not possible based on MDT assessment, a biopsy of the primary tumor site confirming the presence of invasive cancer in the absence of radiographic progression per RECIST 1.1 by BICR is sufficient evidence alone to fulfill the criteria for an event/treatment failure.

Table 16 Case Scenarios for Residual Disease at the Primary Tumor Site

Scenario Number	Radiographic Progression per RECIST 1.1 by BICR	Biopsy	Surgery	Oncology Assessment
1	Pos or neg	Pos	Pos	Event
2	Neg	Pos if completed ≥12 weeks post CRT	Not done or inoperable	Event
3	Pos	Pos	Not done or inoperable	Event
4	Pos	Not done	Not done or inoperable	Event
5	Pos or neg	Neg or Not done	Pos	Event
6	Pos or neg	Pos	Neg	No Event
7	Neg	Neg	Not indicated or Not done	No Event
8	Pos	Neg	Not done or inoperable	No Event
9	Pos or Neg	Neg or Not done	Neg	No Event
10	Neg	Not done	Not done	No Event

BICR=blinded independent central review; CRT=chemoradiotherapy; Neg=negative; Pos=positive; RECIST= Response Evaluation Criteria in Solid Tumors.

Criteria for events of neck lymph node dissection:

Figure 2 indicates the management of the neck lymph nodes based on local radiological assessment of response observed on FDG-PET/CT scan obtained 12 weeks after completion of CRT. When neck dissection is indicated as per Figure 2, this procedure should be completed ≤20 weeks after completion of CRT as per Section 7.1.4.2.

As per Section 7.1.10.3, a neck lymph node dissection or surgery performed in the absence of clinical or radiographic progression ≤20 weeks from the end of CRT is not an event/local failure if neck disease is completely resected. This is regardless of whether invasive cancer is present based on local pathological assessment. Neck dissection or surgery completed >20 weeks from end of CRT is an event if invasive cancer is found to be present based on local pathological assessment (Section 8.4.1.1).

Neck dissection completed at any time based on clinical progression or radiographic findings of progressive disease meets criteria for an event/progressive disease provided the local pathology report confirms the presence of invasive cancer.

If subject proceeds to neck dissection and involved lymph nodes cannot be completely resected at time of neck dissection, this is an event irrespective of timing of neck dissection (Section 7.1.10.3).

If a biopsy is done <12 weeks post CRT and confirms residual invasive cancer, it is only an event if there is also radiographic progression per RECIST 1.1 by BICR.

If a subject is not able to undergo a neck dissection that is indicated, a biopsy of a neck lymph node confirming the presence of invasive cancer in the absence of radiographic progression per RECIST 1.1 by BICR completed ≥12 weeks post CRT is sufficient evidence alone to fulfill the criteria for an event/treatment failure.

The development of any new positive nodes not present at baseline or recurring/progressing nodes will be considered evidence of regional progression (Section 7.1.10.3). If there is radiographic progression per RECIST 1.1 by BICR, this is not an event if subsequent biopsy OR neck dissection is negative for invasive cancer per Table 17 through Table 19.

Case scenarios for neck dissection

Table 17 Case Scenarios for Neck Dissections Completed ≤20 Weeks After Completion of CRT With **NO** Evidence of Clinical or Radiographic Progression

Scenario Number	Radiographic Progression per RECIST 1.1 by BICR or Clinical Progression by Physical Exam	Biopsy	Surgery	Oncology Assessment
1	Neg	Pos if completed ≥12 weeks post CRT	Inoperable or Not done	Event
2	Neg	Not indicated or Neg	Pos and incomplete resection of suspected involved LNs	Event
3	Neg	Not indicated or Neg	Pos	No Event*
4	Neg	Not indicated or Neg	Neg	No Event*
5	Neg	Pos	Pos	No Event*
6	Neg	Pos	Neg	No Event*
7	Neg	Not done	Not done	No Event
8	Neg	Neg	N/A	No Event

BICR=blinded independent central review; CRT=chemoradiation therapy; LN=lymph node; N/A=not applicable; Neg=negative; Pos=positive; RECIST=Response Evaluation Criteria in Solid Tumors.
* Neck dissection must be a complete resection of all suspected involved lymph nodes.

Table 18 Case Scenarios for Neck Dissections Completed ≤20 Weeks After Completion of CRT With Evidence of Clinical or Radiographic Progression

Scenario Number	Radiographic Progression per RECIST 1.1 by BICR or Clinical Progression by Physical Exam	Biopsy	Surgery	Oncology Assessment
1	Pos	Pos	Neg	No Event*
2	Pos	Not indicated or Neg	Neg	No Event*
3	Pos	Neg	Not done	No Event
4	Pos	Not indicated or Neg	Pos	Event
5	Pos	Pos	Pos	Event
6	Pos	Pos	Inoperable or not done	Event**
7	Pos	N/A	N/A	Event***

BICR=blinded independent central review; N/A=not applicable; Neg=negative; Pos=positive; RECIST= Response Evaluation Criteria in Solid Tumors.* Neck dissection must be a complete resection of all suspected involved lymph nodes.
**Only an event if:

a. For clinical PD without evidence of radiographic PD, a biopsy performed ≥12 weeks post CRT is positive confirming invasive disease, and the subject is inoperable/surgery not done.
b. For radiographic PD, a biopsy performed regardless of timing is positive confirming invasive disease, and the subject is inoperable/surgery not done.

*** Only an event if evidence of radiographic progression per RECIST 1.1 is assessed by BICR.

Table 19 Case Scenarios for Neck Dissections Completed >20 Weeks After Completion of CRT

Scenario Number	Radiographic Progression per RECIST 1.1 by BICR or Clinical Progression by Physical Exam	Biopsy	Surgery	Oncology Assessment
1	Pos or Neg	Not done or Neg	Pos	Event
2	Pos or Neg	Pos	Pos	Event
3	Neg	Pos	Neg or Inoperable or Not done	Event
4	Pos	Pos	Neg or inoperable or Not done	Event
5	Pos*	Not done	Not done	Event*
6	Pos or Neg	Not done or Neg	Neg	No Event
7	Neg	Not done	Not done	No Event
8	Pos or neg	Neg	Not done	No Event

BICR=blinded independent central review; Neg=negative; Pos=positive; RECIST= Response Evaluation Criteria in Solid Tumors.

*Only an event if evidence of radiographic progression per RECIST 1.1 is assessed by BICR.

Criteria for events of Recurrent disease:

An assessment of recurrent disease meets the criteria for progressive disease, as defined in Section 8.4.1.1, if one of the following criteria are fulfilled (Table 20):

- Radiographic evidence of recurrent disease as per RECIST 1.1 by BICR and biopsy is not done and/or not indicated.
- Radiographic evidence of recurrent disease as per RECIST 1.1 by BICR and subsequent biopsy confirms evidence of invasive cancer based on local pathological assessment.
- A biopsy confirming invasive cancer at the site of recurrence regardless of whether radiographic progression as per RECIST 1.1 is assessed by BICR.

Table 20 Case Scenarios for Recurrent Disease

Scenario Number	Radiographic Progression per RECIST 1.1 by BICR	Biopsy	Oncology Assessment
1	Pos or Neg	Pos	Event
2	Not done	Pos	Event
3	Pos	Not done	Event
	Not done	Neg	No Event
5	Neg	Neg or Not done	No Event
6	Pos	Neg	No Event

BICR=blinded independent central review; Neg=negative; Pos=positive; RECIST= Response Evaluation Criteria in Solid Tumors.

Criteria for Events of Distant Metastases

An assessment of metastatic disease meets the criteria for progressive disease, as defined in Section 8.4.1.1, if one of the following criteria are fulfilled (Table 21):

- Radiographic evidence of metastatic disease as per RECIST 1.1 by BICR and biopsy is not done and/or not indicated.
- Radiographic evidence of metastatic disease as per RECIST 1.1 by BICR and subsequent biopsy confirms evidence of invasive cancer based on local pathological assessment.
- A biopsy confirming invasive cancer at the site of metastasis regardless of whether radiographic progression as per RECIST 1.1 is assessed by BICR.

Table 21 Case Scenarios for Metastatic Disease.

Scenario Number	Radiographic Progression per RECIST 1.1 by BICR	Biopsy	Oncology Assessment
1	Pos or Neg	Pos	Event
2	Not done	Pos	Event
3	Pos	Not done	Event
4	Not done	Neg	No Event
5	Neg	Neg or Not done	No Event
6	Pos	Neg	No Event

BICR=blinded independent central review; Neg=negative; Pos=positive; RECIST= Response Evaluation Criteria in Solid Tumors.

7.1.5 Tumor Tissue Collection

HPV

Subjects must have assessment of HPV status from tumor tissue prior to randomization (see Section 5.1.2). HPV stratification in this trial may be performed using local testing of HPV status in subjects with oropharynx cancer using the specified method.

Note: 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.

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

Note: Oral cavity, hypopharyngeal, and larynx cancer are not required to undergo local HPV testing by p16 IHC as by convention these tumor locations are assumed to be HPV-negative.

NOTE: However, a tissue sample (regardless of tumor location: oropharyngeal, oral cavity, hypopharynx, or larynx cancer) should be sent to the central vendor for testing and can be the same tissue sample used for PD-L1 (see central laboratory manual).

PD-L1

All subjects will submit either a core or excisional biopsy (fine needle aspirate [FNA] is not adequate) to a central lab for characterization of PD-L1 status.

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

Detailed instructions for tissue collection, processing and shipment are provided in the central laboratory manual.

7.1.6 Patient Reported Outcomes (PROs)

The EQ-5D, EORTC QLQ-C30, and EORTC QLQ-H&N35 PRO questionnaires will be administered on an electronic PRO (ePRO) tablet by trained site personnel and completed electronically by subjects in the following order: EQ-5D first, then EORTC QLQ-C30, and lastly the EORTC QLQ-H&N35 at the time points specified in the Trial Flow Chart. It is a best practice and strongly recommended that ePROs are administered to randomized subjects prior to drug administration, adverse event evaluation, and disease status notification. If the subject does not complete the ePROs for any reason, the Miss Mode form must be completed to capture the reason the assessment was not performed. See protocol-specific guidance in the ePRO manual. Since completion of the final efficacy analysis, any additional ePROs are no longer required to be collected by the Sponsor.

7.1.7 Other Procedures

7.1.7.1 Withdrawal/Discontinuation

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

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.7.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research. Subjects 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 subject'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 subject 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 (e.g., 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 subject’s personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

7.1.7.1.2 Lost to Follow-up

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

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

7.1.7.2 Subject Blinding/Unblinding

TRIAL TREATMENT IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE SUBJECT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND THE SUBJECT UNLESS NECESSARY.

For emergency situations where the investigator or delegate needs to identify the drug used by a subject and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or delegate the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a subject's treatment assignment, the investigator or delegate must enter the toxicity grade of the adverse experiences observed, the relation to study drug, the reason thereof, etc., in the medical chart etc.

Following Sponsor consultation, patients may be unblinded if they have biopsy-proven disease progression and this information is required to guide future treatment decisions for the patient.

For trials that require non-emergency unblinding as part of the trial design (eg, in cases of biopsy proven disease progression in this trial) to support treatment decisions, IVRS should be used to unblind the subject. The emergency unblinding center should not be used for this purpose.

Subjects whose treatment assignment has been unblinded by the investigator/delegate and/or non-study treating physician should continue to be monitored in the trial.

Additionally, the investigator must go into the IVRS system and perform the unblind in the IVRS system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this trial, IVRS/IWRS should be used for emergency unblinding in the event that this is required for subject safety.

Treatment/Vaccine identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the subject.

7.1.7.3 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 trial 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 trial site.

See protocol-specified guidance in the study-specific Investigator Trial File Binder (ITFB), Pharmacy Manual, central laboratory manual, and Site Imaging Manual.

7.1.7.4 Domiciling

At the discretion of the investigator, subjects may report to the clinical research unit (CRU) the evening prior to the schedule day of cisplatin administration and remain in the unit until 24 hours post-dose to ensure proper hydration.

7.1.8 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.8.1 Screening

Within 28 days prior to randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

Results of a test or procedure prior to the subject providing informed consent as part of routine clinical management are acceptable in lieu of a screening test or procedure if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of trial treatment except the following:

- Laboratory tests and ECOG Performance Status (PS) are to be performed within 10 days prior to the first dose of trial treatment. ECOG PS must be 0 or 1 on the first day of dosing.
- For women of reproductive potential, a serum pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. A urine test may be considered if serum test is not appropriate.
- CrCl during screening is required within 10 days prior to treatment initiation and should be assessed prior to randomization. It does not need to be repeated within 24 hours prior to treatment initiation (Treatment 1: Cycle 1, Day 1), unless clinically indicated. CrCl must be repeated within 24 hours prior to start of each cisplatin administration for management of dose reduction for renal toxicity guidelines.
- Tumor sample collection (not required to be obtained within 28 days prior to the first dose of trial treatment).
- Documented routine oral and dental check-up (including radiological examination with teeth extraction if needed) are acceptable within 6 weeks prior to trial treatment to avoid feeling dental artifacts.
- Documented routine neurological exam is acceptable within 6 weeks prior to trial treatment.

- Documented routine fiberoptic exam and endoscopy of upper-aerodigestive tract is required for all subjects during screening. Biopsies of the primary lesion(s) are also required if appropriate. Associated photographs and/or drawing of the finding(s) are acceptable within 8 weeks of trial treatment.
- Documented routine audiometry tests are acceptable within 6 weeks of trial treatment.

The subject's documented informed consent to undergo screening for the clinical trial must be given prior to the performance of any protocol laboratory/imaging tests that are not part of local routine guidelines.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria are met.

7.1.8.2 Treatment Period

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided in Section 7.1 – Trial Procedures.

Treatment 1 includes pembrolizumab/placebo priming, CRT plus two pembrolizumab/placebo doses. Treatment 2 includes pembrolizumab/placebo maintenance dosing and post-CRT follow-up (Year 1) procedures.

Subjects who did not receive all pembrolizumab/placebo doses in Treatment 1 may make up these missed doses in Treatment 2 to ensure all 17 doses are administered. Pembrolizumab/placebo doses administered after CRT completion are considered part of Treatment 2 maintenance phase.

7.1.8.3 Post-Treatment Visits

7.1.8.3.1 End-of-Treatment Visit

The End of Treatment visit should occur at the time trial treatment is completed or discontinued for any reason. If the End of Treatment visit occurs 30 days from the last dose of trial 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 should be performed. Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

Subjects who discontinue trial treatment for a reason other than an event/disease progression, withdrawal of consent, or starting a new anticancer therapy will still be considered on study and should continue with scheduled assessments (also refer to Section 5.10.1).

7.1.8.3.2 Safety Follow-up Visit

The mandatory 30-Day Safety Follow-Up Visit should be conducted 30 days after the last dose of trial treatment or before the initiation of a new anticancer treatment, whichever comes first. All AEs that occur prior to the 30-Day Safety Follow-Up Visit should be recorded.

Additionally, subjects in Post-Treatment Follow-Up will be followed for treatment-related late toxicities meeting serious criteria for up to 5 years and should be recorded.

7.1.8.3.3 Efficacy Follow-up Visits

Subjects who complete trial treatment (all 17 doses of pembrolizumab/placebo) or discontinue trial treatment for a reason other than an event/disease progression or starting a new anticancer therapy will move into the Post-Treatment Efficacy Follow-Up Phase and should be assessed every 3 months (91 ± 7 days) for Follow-Up Years 1 through 3 and every 6 months (± 14 days) for Follow-Up Years 4 through 5 and every 6 months (± 28 days) after Year 5 after randomization by radiologic imaging to monitor disease status as well as all assessments, as outlined in the Post-treatment Efficacy Follow-up Visits trial flow chart (see Section 6.3 and Table 22 below). The radiologic imaging and all assessments and procedures noted in the trial flow chart should be conducted on the same day (or if on different days should stay on the same schedule) with a clock start date of last dose of CRT. The clock will start at the end of CRT (i.e., last dose of CRT). All follow-up visits should stay on track using the last dose of CRT as the starting clock, i.e., if one of the follow-up visits is delayed, the subject will stay on the original schedule starting with the last dose of CRT for all future visits. The schedule should not be recalculated.

For subjects who discontinue study treatment early, the remainder of their post-treatment follow-up for the 1st year should be completed as specified in Follow-up 1. These subjects should remain in Follow-up 1 for up to a total of 2 years (Table 22).

Table 22 Post-Treatment Follow-up Phase Schedule

Follow-up 1	Follow-up 2	Follow-up 3	Follow-up 4	After Year 5
Remainder of Year 1 for subjects who discontinued Pembrolizumab/ Placebo treatment prior to completion of Year 1				
Follow up Year 2	Follow up Year 3	Follow up Year 4	Follow up Year 5	Follow up after Year 5
Assessed every 3 months (± 7 days) to monitor disease status	Assessed every 3 months (± 7 days) to monitor disease status	Assessed every 6 months (± 14 days) to monitor disease status	Assessed every 6 months (± 14 days) to monitor disease status	Assessed every 6 months (± 28 days) to monitor disease status

7.1.8.3.3.1 Imaging Follow-Up Visits

Subjects who complete trial treatment (all 17 doses of pembrolizumab/placebo) or subjects who discontinue trial treatment without a documented event/disease progression as described in Section 5.10.1, should continue with imaging and other clinical assessments per the protocol-defined 3- and 6-month visit schedule until: 1) an event/disease progression, 2) death, 3) withdrawal of consent or 4) study conclusion or early termination, whichever occurs first.

Information regarding post-study anticancer treatment will be collected if new treatment is initiated.

7.1.8.3.4 Survival Follow-up Assessments

Once a subject experiences an event/disease progression as defined in the EFS Section 8.4.1.1, the subject enters the Survival Follow-Up Phase and should be contacted by telephone or have their medical records reviewed every 3 months (±7 days) during Follow-Up Years 1 through 3 and every 6 months (±14 days) during Follow-Up Years 4 through 5 and every 6 months (±28 days) after Follow-Up Year 5 to assess for survival status until death, withdrawal of consent or the end of the study, whichever occurs first. Assessment of overall survival should also include evaluation for whether other anticancer therapy has been initiated. When assessing for survival status for subjects in survival follow-up who have not yet experienced an event/PD, also evaluate for whether the subject has had additional imaging assessments or experienced biopsy and/or surgery confirmed progression. 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 interim analyses and final analysis. All subjects 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 or have their medical records reviewed at that time. These additional assessments will have no effect on the schedule for the protocol-specified Survival Follow-Up Phase, i.e., the schedule for Survival Status (see Section 6.3 - Post-Treatment Efficacy Follow-up Visits) will continue as planned whether or not an additional survival status assessment is conducted.

7.1.9 Criteria of Evaluation

7.1.9.1 Evaluation of Efficacy

Objective tumor response and time to progression will be measured according to the RECIST 1.1 criteria [27], Section 12.7.

Response criteria are essentially based on a set of evaluable lesions (including measurable and non-measurable lesions) identified at baseline as target lesions, and/or non-target lesions, which are followed until disease progression. When the investigator identifies radiographic progression per RECIST 1.1, the central imaging vendor will perform expedited verification of radiologic PD and communicate the results to the trial site and Sponsor. Treatment/post-treatment follow-up should continue until PD has been verified or an event has occurred, death, withdrawal of consent, study conclusion or early termination, whichever occurs first.

The following paragraphs are a quick reference to the RECIST criteria (version 1.1). The complete criteria are included in the published RECIST document (available at http://www.eortc.be/RECIST.

7.1.9.2 Measurability of Tumor Lesions at Baseline

7.1.9.2.1 Definitions

- Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- Measurable lesions - tumor lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) and as ≥10 mm with CT scan or clinical examination [using calipers]. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component >10 mm by CT scan). Malignant lymph nodes must be ≥15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters) by use of a ruler or calipers. Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.
- Non-measurable lesions - All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Nodes that have a short axis <10 mm at baseline are considered non-pathological and should not be recorded or followed.
- Target Lesions. When more than one measurable tumor lesion or malignant lymph node is present at baseline all lesions up to a maximum of 10 lesions total (and a maximum of 5 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Note that pathological nodes must meet the criterion of a short axis of ≥15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 10 is to be calculated and recorded.
- Non-target Lesions. All non-measurable lesions (or sites of disease) including pathological nodes (those with short axis ≥10 mm but <15 mm), plus any measurable lesions over and above those listed as target lesions are considered non-target lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as “present” or “absent”.

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

7.1.9.3 Methods of Measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy, which may be treatment arm dependent. While on study, all target lesions recorded at baseline should have their actual measurements recorded on the CRF at each subsequent evaluation, even when very small (e.g., 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split, add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

- Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.
- Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions.
- CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans). While PET scans are not considered adequate to measure lesions, FDG-PET CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).
- Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT must be obtained.
- Endoscopy. The utilization of these techniques for objective tumor evaluation is not allowed. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.
- Cytology, Histology. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the

neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

7.1.9.4 Frequency of Tumor Re-evaluation

Baseline assessments: Physical examination including head and neck examination, contrast enhanced CT scan of head and neck, chest, and upper abdomen (to cover liver in its entirety) or head and neck and upper abdomen MRI and chest CT-scan. FDG/PET scan is an option to replace the chest CT-scan.

Tumor evaluation: Physical examination to assess tumor status and toxicity will be performed every 3 months for 3 years; after year 3, physical examination will be performed every 6 months until year 5. Imaging after 5 years should be done every 6 months (± 28 days).

Tumor imaging: disease evaluation will be performed by contrast enhanced CT scan of head and neck, chest and upper abdomen or head and neck and upper abdomen MRI and chest CT scan 12 weeks (± 7 days) after the end of CRT and then every 3 months (± 7 days) during the first 3 years since randomization. During the fourth and fifth Efficacy Follow-Up years, imaging will be performed every six months (± 14 days). Imaging after 5 years should be done every 6 months (± 28 days). 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. 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, death, withdrawal of consent, study conclusion or early termination, whichever occurs first.

Note: The imaging schedule start time begins on the last day of CRT. Years 1-5 and thereafter in the Post-Treatment Follow-up year (Follow-up 1 through Follow-up 4 and thereafter) start time begins at randomization, and the imaging schedule visits should be conducted at the same time as the post-treatment follow-up visits.

Evaluation of the neck for potential neck dissection: Neck imaging (MRI or CT-scan) and FDG-PET/scan will be performed at week 12 (±7 days) after the end of CRT to evaluate the neck in the context of potential neck dissection. Neck dissection will be recommended in case of persistent disease in the neck and should be performed before the end of Week 16 after the last dose of CRT but could be performed out to Week 20 after the last dose of CRT.

7.1.9.5 Date of Event/Progression

This is defined as the date of the first of the following events:

- The first day when the RECIST (version 1.1) criteria for PD are met.
- The first day there is pathological confirmation from surgery or biopsy of progressive and/or residual invasive cancer.
- Date of death due to any cause.

Refer to Ref 51 as well as above for further information on what constitutes early progression, assessment of progression of non-target disease, new lesions and usage of FDG-PET to diagnose progression.

7.1.9.6 Event-Free Survival

Event-free survival is defined as the time from the date of randomization to the date of first record of any of the following events:

Progression per RECIST 1.1 by BICR or biopsy as indicated for:

- Locoregional progression or recurrence
- Distant metastasis

Surgery:

- Salvage surgery for persistent or residual disease at the primary tumor site requiring surgical removal when invasive cancer is present on final pathology
    - If salvage surgery of the primary tumor site cannot be performed, biopsy completed 12 or more weeks following completion of CRT is an event if invasive cancer is present.
- Neck dissection or surgery (performed for clinical or radiological disease progression per RECIST 1.1) ≤20 weeks from end of CRT when invasive cancer is present
- Neck dissection or surgery >20 weeks from end of CRT when invasive cancer is present
    - If neck dissection or surgery cannot be performed, biopsy completed 12 or more weeks following completion of CRT is an event if invasive cancer is present.

Death due to any cause

7.1.9.7 Local Regional Control

Time to locoregional failure is defined as the time from the date of randomization to the date of the first record of appearance of local or regional progression/recurrence, to the date of neck dissection ≤20 weeks performed for clinical or radiological (RECIST 1.1) disease progression from end of CRT when invasive cancer is present, to the date of neck dissection >20 weeks from end of CRT when invasive cancer is present, or to the date of salvage surgery of primary tumor when invasive cancer is present performed for clinical or radiological (RECIST 1.1) disease progression, whichever comes first. When neck dissection or salvage surgery of the primary tumor site is indicated but not possible, date of locoregional failure can be defined as the date of biopsy that confirms presence of invasive cancer.

Distant recurrence/progression diagnosed before locoregional failure and death in absence of locoregional failure are not considered events of interest, but as competing risks events in the analysis of this endpoint.

7.1.9.8 Distant Metastasis Free Survival

Distant metastasis free survival is defined as the time from the date of randomization to the date of first record of appearance of distant metastasis or death for any cause. Locoregional failure or second cancers diagnosed before the distant metastases are not considered events of interest for this endpoint.

7.1.9.9 Overall Survival

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

7.1.10 Assessment of Response

7.1.10.1 Measurement of Response

Due to the difficulties in objectively assessing response following chemoradiation, response will not be a study endpoint, but measurements will be recorded to assist with determination of progressive disease and locoregional failure status. Measurements will be taken from CT or MRI and the same method should be used to follow subjects unless medically contraindicated. All subjects will have a clinical and radiological (CT or MRI and FDG-PET or FDG-PET/CT) assessment at Week 20 (12 weeks post-completion of CRT) as defined in Section 7.1.4.

7.1.10.2 Local Failure

Local failure will be primarily determined by evidence of progression or recurrence clinically or radiologically. For clinical and radiographic assessments, RECIST 1.1 criteria for progressive disease shall be used whenever applicable (see Section 7.1.9). In the case of nonmeasurable disease or in circumstances where laryngeal oedema complicates the interpretation of radiological measurements, unequivocal clinical description of disease progression is required. Biopsy proof of progressive disease is desirable but is not essential if progression documented. Any form of salvage surgery at the primary site after 12 weeks post CRT will be considered either local or regional progression unless the pathology shows no evidence of disease. If a subject has a biopsy result showing disease at the primary site at the time of or beyond 12 weeks after completion of CRT, this can be used as evidence for local failure, even if no other evidence of progression has been documented.

7.1.10.3 Regional Failure

If neck disease cannot be completely resected at neck dissection, this will be deemed to be regional failure. If they have completely resected positive nodes from a neck dissection performed in the absence of clinical or radiographic progression ≤20 weeks after completion of CRT, they will not be considered to have experienced regional progression since the neck dissection completed within this timeframe is part of the pre-determined treatment package.

Subjects who do not have a neck dissection because their neck disease is judged to be unresectable will only be deemed to have failure in the neck after biopsy or cytological confirmation is obtained or disease progression is documented. Regardless of the neck

management chosen, if he/she undergoes salvage neck dissection at any time based on clinical or radiographic findings of progressive disease, then the subject meets the criteria for regional failure provided the pathology report confirms the presence of cancer.

Development of any new positive nodes not present at baseline or recurring/progressing nodes will be considered evidence of regional progression.

7.1.10.4 Locoregional Failure

This is defined as local failure, regional failure, or both. For the purposes of determining site of first failure, the category of both will be applicable if local and regional failure occurs within one month of each other.

7.1.10.5 Distant Failure

This is defined as the presence of positive pathological or radiological evidence of recurrent disease at any site of the body with the exception of those defined as ‘local’ or ‘regional’.

When distant metastases are the first indication of relapse, then the subject must be examined for locoregional disease.

7.1.11 Post-CRT Neck Surgery

7.1.11.1 Neck Dissection

Participating centres will be required to adhere to the following policies regarding post-CRT neck dissection in subjects who have achieved a complete response at the primary site.

No neck surgery may be performed before the post-CRT assessment in Week 20 from randomization (12 weeks following completion of CRT) unless there is evidence of progressive disease. Subjects who achieve a complete clinical and complete metabolic response as assessed by FDG-PET or FDG-PET/CT in Week 12 post-completion of RT **will not** have any neck dissection. Those subjects with a residual nodal mass and evidence of metabolic activity on FDG-PET or FDG-PET/CT at that time should proceed immediately to neck dissection. Any residual metabolically inactive mass may be observed for continued regression with the FDG-PET or FDG-PET/CT being repeated at 3 monthly intervals up to 9 months post-CRT or follow local institutional guidelines. If the nodal mass ceases regressing or begins to grow and/or a subsequent FDG-PET or FDG-PET/CT scan shows metabolic activity the subject **must** proceed to neck dissection. If the subject has a residual nodal mass with short axis >1 cm but <2 cm at 9 months post-CRT that remains static in size and FDG-PET or FDG-PET/CT negative, it may be continued to be observed.

The extent of neck dissection may be selective or comprehensive according to the initial extent of nodal disease. In subjects with limited nodal disease pre-treatment, a selective neck dissection is preferred.

7.1.11.2 Salvage Neck Dissection

Salvage neck dissection for recurrent disease (after achieving a complete response in the neck) may be undertaken at any time according to clinical indications.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an adverse event.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets.

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.

The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.4.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the Electronic Data Capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definitions of Medication Error, Misuse, and Abuse

Investigators need to document if an SAE is associated with a medication error, misuse, or 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 participant.

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.

7.2.2 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

For this trial, an overdose will be defined as ≥1000 mg (5 times the dose) of pembrolizumab and as any dose ≥20% over the prescribed dose for the CRT treatments. No specific information is available on the treatment of an overdose of pembrolizumab. In the event of overdose, the subject 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

There is no specific antidote for radiation overdose. In the event of an overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Reporting of Overdose to the Sponsor

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial.

Pregnancies and lactations of subjects and female partners of male subjects from the time the documented informed consent form is provided but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations of subjects and female partners of male subjects that occur from the time of treatment allocation/randomization through 180 days following cessation of Sponsor's product must be reported. 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.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.4 Immediate Reporting of Adverse Events to the Sponsor

7.2.4.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: 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.

Refer to Table 23 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.4.3 for additional details), that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject 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, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of trial treatment, or 30 days following cessation of trial treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.4.3 for additional details), whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

All serious adverse events 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.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor. Subjects in post-treatment follow-up will be actively followed for treatment-related late serious adverse events for up to 5 years.

All subjects with serious adverse events must be followed up for outcome.

7.2.4.2 Events of Clinical Interest

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

For the time period beginning when the consent form is documented until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject 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, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to

the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, 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).

7.2.4.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 7.2.3.

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

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

7.2.5 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events 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.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

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 (i.e., 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 experience to the single agent.

Table 23 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient 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.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product 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 drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to 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

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(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 SPONSOR'S PRODUCT, OR IF REEXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.6 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 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.

7.3.2 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.

7.3.3 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 external Data Monitoring Committee (eDMC) regarding the trial.

7.3.4 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 (e.g., 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 subject 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 8.7 - 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 Sponsor protocol team; meeting

facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DMC. The DMC will monitor the trial at an appropriate frequency, as described in the detailed DMC charter. The DMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

An eDMC recommendation will be communicated to the EOC as agreed to in the DMC Charter.

8.0 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 (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Separate analysis plans may be developed for PK/modeling analysis, biomarker analysis, and genetic data analysis. Post hoc exploratory analyses will be clearly identified in the CSR. The analysis plan for ePRO assessments will be included in the sSAP.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2-8.12.

Study Design Overview	This is a randomized, double-blind, multicenter Phase III trial to evaluate efficacy and safety of pembrolizumab in combination with CRT versus placebo in combination with CRT in subjects with locally advanced HNSCC.
Treatment Assignment	Approximately 780 subjects will be randomized 1:1 into the following two treatment arms: Arm 1 will receive the combination therapy of pembrolizumab 200 mg administered intravenously (IV) every 3 weeks (Q3W) in combination with CRT; Arm 2 will receive placebo Q3W in combination with CRT. Stratification factors are provided in Section 5.6. This study will be conducted as a double-blind study under in-house blinding procedures.
Analysis Populations	Efficacy: Intention to Treat (ITT) Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	Event-free survival (EFS)
Key Secondary Endpoints	Overall survival (OS)
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	The primary hypotheses for EFS will be evaluated by comparing pembrolizumab in combination with CRT to placebo in combination with CRT using a stratified log-rank test. Estimation of the hazard ratio 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.

Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. In this trial, no adverse events of interest warrant inference testing as Tier 1 events. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals (CI) provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. The 95% confidence intervals for the between-treatment differences in percentages will be provided using the Miettinen and Nurminen method with sample size weighting scheme.
Interim Analyses	**Efficacy** One interim efficacy analysis will be performed in this study. Results will be reviewed by an external data monitoring committee (eDMC). The interim and final analysis timing and purpose is summarized below. Details are provided in Section 8.7. • IA o Timing: at least 353 EFS events and all subjects have been followed up for at least 23 months (~86% of the final required EFS events, estimated to be 48 months after study start). o Testing: Inferential analyses of EFS will be provided. • FA o Timing: at least 410 EFS events and all subjects have been followed up for at least 35 months (estimated to be 60 months after study start). o Testing: Inferential analyses of EFS will be provided. Note that if the EFS events accrue slower than expected, the analysis can be delayed up to 3 months after the projected timing, i.e., the Sponsor may conduct the IA and FA with additional 3 months of follow-up, or the specified number of events is observed, whichever occurs first. **Safety** One interim safety analysis will be performed when the first 30 subjects have completed CRT. The eDMC will also review safety data periodically in the study.
Multiplicity	The Type I error rate for the EFS and OS hypotheses is strongly controlled at 2.5% (1-sided). A group sequential approach will be used to allocate alpha between the interim and final analyses of EFS. The study will be considered a success if EFS in all subjects is demonstrated to be statistically significant under multiplicity control. If the statistical criterion for success in the primary EFS hypothesis is met at the interim analysis or final analysis, the secondary OS hypothesis will be tested in all subjects.
Sample Size and Power	The planned sample size is approximately 780 subjects. For EFS, the trial has 94.6% power to demonstrate that pembrolizumab in combination with CRT is superior to placebo in combination with CRT at an overall one-sided 2.5% alpha-level, if the true hazard ratio is 0.7.

8.2 Responsibility for Analyses/In-House Blinding

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

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

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented in an interactive voice response system (IVRS).

The investigator will be blinded to subject-level biomarker results. 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 8.7.

8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0.

8.4 Analysis Endpoints

8.4.1 Efficacy Endpoints

8.4.1.1 Primary: Event-Free Survival (EFS)

Event-free survival (EFS) is defined as the time from the date of randomization to the date of first record of any of the following events:

Progression per RECIST 1.1 by BICR or biopsy as indicated for:

- Locoregional progression or recurrence
- Distant metastasis

Surgery:

- Salvage surgery for persistent or residual disease at the primary tumor site requiring surgical removal when invasive cancer is present on final pathology
    - If salvage surgery of the primary tumor site cannot be performed, biopsy completed 12 or more weeks following completion of CRT is an event if invasive cancer is present.
- Neck dissection or surgery (performed for clinical or radiological disease progression per RECIST 1.1) ≤ 20 weeks from end of CRT when invasive cancer is present

- Neck dissection or surgery >20 weeks from end of CRT when invasive cancer is present
    - If neck dissection or surgery cannot be performed, biopsy completed 12 or more weeks following completion of CRT is an event if invasive cancer is present.

Death due to any cause.

The criteria for an EFS event are comprehensively defined in Section 7.1.4.3. See Section 8.6.1 for the censoring rules.

8.4.1.2 Secondary: Overall Survival (OS)

Overall survival (OS) is defined as the time from randomization to death due to any cause.

8.4.2 Safety Endpoints

Safety endpoints are described in Sections 4.2.3.2.

8.4.3 Patient Reported Outcome (PRO) Endpoints

The following key PRO endpoints will be evaluated as described in Section 4.2.3.3:

- EORTC QLQ-C30: global health status/QoL and physical functioning
- Symptom sub-scale and single item scores from EORTC QLQ-H&N35 including the following:
    - problems with swallowing
    - problems with speech
    - pain in the mouth

Additional scales of EORTC QLQ-C30/QLQ-H&N35 and exploratory PRO endpoints as described in Section 4.2.3.3 will be evaluated. Details will be provided in the sSAP.

8.5 Analysis Population

8.5.1 Efficacy Analysis Population

The Intention-to-Treat (ITT) population will serve as the population for the primary efficacy analyses. All randomized subjects will be included in this population. Subjects will be analyzed in the treatment group to which they are randomized.

8.5.2 Safety Analysis Population

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least 1 dose of study treatment. Subjects will be analyzed in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who take incorrect study treatment for the entire treatment period will be included in

the treatment group corresponding to the study treatment actually received. Any subject who receives the incorrect study medication for one cycle but receives the correct treatment for all other cycles will be analyzed according to the correct treatment group and a narrative will be provided for any events that occur during the cycle for which the subject is incorrectly dosed.

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 each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.5.3 PRO Analysis Population

The PRO analyses are based on the PRO full analysis set (FAS) population, defined as subjects who have at least one PRO assessment available for the specific endpoint and have received at least one dose of study medication. Subjects will be analyzed in the treatment group to which they were randomized.

8.6 Statistical Methods

8.6.1 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 8.8, Multiplicity. Nominal p-values may be computed for other efficacy analyses but should be interpreted with caution due to potential issues of multiplicity.

8.6.1.1 Event-Free Survival

The non-parametric Kaplan-Meier method will be used to estimate the EFS curve in each treatment group. The hypothesis of treatment difference in EFS will be tested by the stratified log -rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to estimate the magnitude of the treatment difference (i.e., 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 (RT regimen, tumor site/p16 status and stage, see Section 5.6 for additional detail) will be applied to both the stratified log-rank test and the stratified Cox model. In the event that there are a small number of events in one or more strata, for the purpose of analysis, strata will be combined to ensure sufficient number of events in each stratum. Details regarding the combining of strata will be specified in the sSAP prior to database lock based on a blinded review of event counts by stratum.

Since disease progression is assessed periodically, disease progression can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is first documented. For the primary analysis, for the subjects who have PD, the true date of the EFS event will be approximated by the date of the first assessment at which PD, surgery, or death is objectively documented.

In order to evaluate the robustness of the EFS endpoint, one primary and three sensitivity analyses with a different set of censoring rules will be performed. The primary analysis

follows the intention-to-treat principle. That is, PD, surgery or death is counted as event regardless of missed study visits or initiation of new anticancer therapy. For the first sensitivity analysis, if the events (PD, surgery or death) are after the initiation of a new anticancer therapy for R/M disease, the data are censored at the last disease assessment prior to the initiation of a new anticancer therapy for R/M disease. The second sensitivity analysis considers initiation of a new anticancer treatment for R/M disease to be an EFS event for subjects without a documented EFS event. The third sensitivity analysis is the same as the primary EFS analysis, with the exception that surgery is not counted as an EFS event. If a subject 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 24.

Table 24 Censoring Rules for Primary and Sensitivity Analyses of EFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2	Sensitivity Analysis 3
PD, surgery or death documented before new anticancer therapy* if any, or new anticancer therapy is not initiated	EFS event at date of documented PD, surgery or death	EFS event at date of documented PD, surgery, or death	EFS event at date of documented PD, surgery or death	EFS event at date of documented PD or death. If no PD and no death, censored at last disease assessment.
PD, surgery or death documented after new anticancer therapy*	EFS event at date of documented PD, surgery or death	If the new anticancer therapy is for R/M disease, then censored at last disease assessment before the initiation of a new anticancer therapy for R/M disease; otherwise, EFS event at date of documented PD, surgery or death	EFS event at date of documented PD, surgery, death, initiation of a new anticancer therapy for R/M disease, whichever occurs first.	EFS event at date of documented PD or death. If no PD and no death, censored at last disease assessment.
No PD, no surgery and no death; new anticancer therapy* is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment
No PD, no surgery and no death; new anticancer therapy* is initiated	Censored at last disease assessment	If the new anticancer therapy is for R/M disease, then censored at last disease assessment before the initiation of a new anticancer therapy for R/M disease; otherwise, censored at last disease assessment	If the new anticancer therapy is for R/M disease, then EFS event at date of the initiation of a new anticancer therapy for R/M disease; otherwise, censored at last disease assessment	Censored at last disease assessment

EFS= event free survival; PD=progressive disease; R/M=recurrent or metastatic.
* The new anticancer therapy in the sensitivity analyses 1 and 2 is defined as any new oncology drugs or radiation for R/M disease.

8.6.1.2 Overall Survival

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The hypothesis of a treatment difference in OS will be tested by the stratified log -rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to estimate the magnitude of the treatment difference (i.e., the HR) for OS. The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization will be applied. In the event that there are a small number of events in one or more strata, for the purpose of analysis, strata will be combined to ensure sufficient number of events in each stratum. Details regarding the combining of strata will be specified in the sSAP prior to database lock based on a blinded review of event counts by stratum.

8.6.2 Summary of Efficacy Analysis Methods

A summary of the analysis strategy for key efficacy endpoints is provided in Table 25.

Table 25 Analysis Strategy for Key Efficacy Endpoints

Endpoint/ Variable	Statistical Method†	Analysis Population	Missing Data Approach
Primary Hypothesis			
EFS	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2 • Sensitivity analysis 3
Secondary Hypotheses			
OS	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at the last date the subject was known to be alive

EFS=event free survival; ITT=intention-to-treat; OS=overall survival.

† Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization (see Section 5.6) will be applied to the analysis model.

8.6.3 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.

AEs will be summarized overall and by the following time periods:

- Period of treatment with pembrolizumab/placebo in combination with CRT
- Period of maintenance with pembrolizumab/placebo
- Follow-up period with no treatment

The analysis of safety results will follow a tiered approach (Table 26). The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as system organ class terms) are either pre-specified as "Tier 1" endpoints or will be classified as belonging to "Tier 2" or "Tier 3" based on the number of events observed.

Tier 1 Events

Safety parameters or adverse events of interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance. There are no Tier 1 events for this protocol as preliminary data from the MISP study [67] has demonstrated an acceptable and manageable safety/tolerability profile of pembrolizumab in combination with CRT for LA HNSCC.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of subjects with events.

Membership in Tier 2 requires that at least 10% of subjects in any treatment group exhibit the specific AE; all other AEs will belong to Tier 3. The threshold of at least 10% of subjects was chosen for Tier 2 events because the population enrolled in this study is in critical condition and usually experiences various AEs of similar types regardless of treatment; events reported less frequently than 10% of subjects would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, 5% of subjects in any treatment group that exhibit a specific serious AE or a specific Grade 3-5 AE will be considered Tier 2 endpoints. Because many 95% CIs for Tier 2 events may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in AEs and laboratory values that meet predefined limits of change.

Tier 3 Events

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

Table 26 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Specific Grade 3-5 AE (incidence ≥5% of subjects in one of the treatment groups)	X	X
	Specific serious AE (incidence ≥5% of subjects in one of the treatment groups)	X	X
	Specific AEs, SOCs (incidence ≥10% of subjects in one of the treatment groups)	X	X
Tier 3	Any AE		X
	Any Serious AE		X
	Any Grade 3-5 AE		X
	Any Drug-Related AE		X
	Any Serious and Drug-Related AE		X
	Any Grade 3-5 and Drug-Related AE		X
	Discontinuation due to AE		X
	Any AE resulting in death		X
	Specific AEs, surgical complications, SOCs (incidence >0% of subjects in one of the treatment groups)		X
	Change from Baseline Results (lab toxicity grade)		X
AE = adverse event; CI=confidence interval; SOC = system organ class.			

8.6.4 Statistical Methods for PRO Analyses: EORTC QLQ-C30 & QLQ-H&N35

The change from baseline in the following secondary QoL outcomes from the EORTC QLQ-C30 and QLQ-H&N35 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

The time point for the mean change from baseline will be determined based on blinded data review prior to the database lock for any PRO analysis and documented in the sSAP. To assess the treatment effects on the quality-of-life outcomes, a constrained longitudinal data analysis (cLDA) 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 treatment difference in terms of least square (LS) mean change from baseline will be estimated from this model together with 95% CI. Model-based LS mean with 95% CI will be provided by treatment group for PRO scores at baseline and post-baseline time point.

Details of PRO analyses will be described in the sSAP.

8.6.5 Summaries of Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant 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 subjects screened and randomized, and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (e.g., age), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

8.7 Interim Analyses

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

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.

8.7.1 Efficacy Interim Analyses

A summary of interim and final analyses strategy for efficacy is provided in Table 27.

Table 27 Summary of Interim and Final Analyses Strategy for Efficacy

Analyses	Key Endpoints	Timing†	Estimated Months after First Subject Randomized	Primary Purpose of Analysis
Efficacy IA	• EFS • OS	At least 353 EFS events have been observed and all subjects have been followed up for at least 23 months	~48 months	• Demonstrate EFS superiority • Evaluate OS superiority
Efficacy FA	• EFS • OS	At least 410 EFS events have been observed and all subjects have been followed up for at least 35 months	~60 months	• Demonstrate EFS superiority (if not significant at IA) • Evaluate OS superiority

EFS = event-free survival; FA = final analysis; IA = interim analysis; OS = overall survival.
† Note: For efficacy IA and FA, if the EFS events accrue slower than expected, the analysis can be delayed up to 3 months after the projected timing, i.e., the Sponsor may conduct IA and FA with additional 3 months of follow-up, or the specified number of events is observed, whichever occurs first.

Decisions to stop the study early will be based on eDMC 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 subjects for survival update.

Type I error control for the efficacy analyses as well as efficacy bounds are described in Section 8.8 - Multiplicity.

8.7.2 Safety Interim Analyses

A summary of interim analysis strategy for safety is provided in Table 28.

Table 28 Summary of Interim Analyses Strategy for Safety

Key Endpoints	Timing	Estimated Months after First Subject Randomized	Primary Purpose of Analysis
AEs	• First 30 subjects have completed Treatment 1 (concurrent CRT) phase • Every 4 months after the first planned safety IA for 1 year • Every 6 months thereafter and/or at the appropriate frequency as outlined by the eDMC. Details will be included in the DMC charter.	• ~5 months • ~9, 13 months • ~19, 25, etc. (every 6 months and/or at the appropriate frequency as specified in the DMC charter)	Safety evaluation

AE=Adverse Event; CRT=Chemoradiation therapy; DMC=Data Monitoring Committee; eDMC=external DMC; IA=interim analysis.

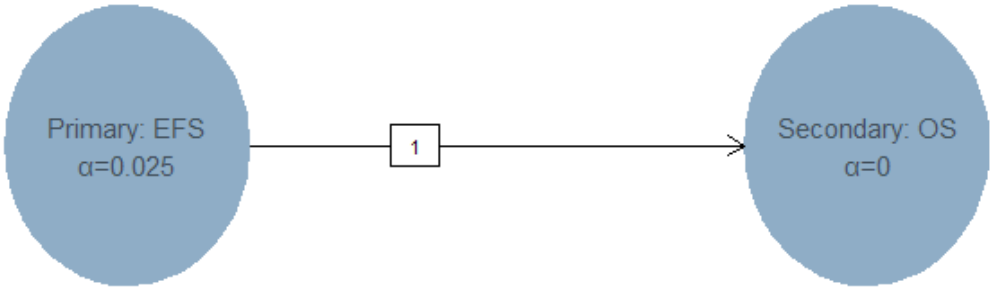
8.8 Multiplicity

8.8.1 Multiplicity Control for Efficacy Analyses

The overall Type I error for testing the EFS and OS hypotheses is strongly controlled at α=2.5% (1-sided) by using a fixed sequential testing procedure in the order of EFS and OS. If the statistical criterion for success in the primary EFS hypothesis is met at the interim analysis or final analysis, the secondary OS hypothesis will be tested in all subjects.

Figure 3 shows the initial one-sided α-allocation for each hypothesis in the ellipse representing the hypothesis. The weight for reallocation from the EFS hypothesis to OS is represented in the box on the line connecting hypotheses. This is further explained below.

Figure 3 Multiplicity Schema



Event-Free Survival

The EFS hypothesis will be tested at α = 0.025. Table 29 below shows the bounds and boundary properties for each analysis of EFS which were derived using a Lan-DeMets O'Brien-Fleming alpha-spending function. Note that the final row of the table indicates the total power to reject the null hypothesis. Also, note that the bounds and nominal alpha levels provided in Table 29 are based on the assumption that the number of EFS events at IA and FA are 353 and 410, respectively. At the time of IA, the observed number of events may differ substantially from the expected. To avoid overspending at the IA and leave reasonable alpha for the FA, the minimum alpha spending strategy will be adopted. At the IA, the information fraction used in Lan-DeMets spending function to determine the alpha spending at the IA will be based on the minimum of the expected information fraction and the actual information fraction at the time of the analysis. Specifically,

- In the scenario that the event accumulation is faster than expected, i.e., if the number of observed events exceeds the pre-specified number of events at IA, then the information fraction will be calculated as the pre-specified number of events at IA over the target number of events at FA, and hence the alpha spending at IA will not exceed the pre-specified level based on the pre-specified number of events, as shown in the table below.
- In the scenario that the event accumulation is slower than expected and the number of events is less than the pre-specified number of events in the table when IA is conducted, the bounds will be adjusted using the spending functions accordingly, with information fraction calculated as the actual number of events at IA over the target number of events at FA.

The final EFS analysis will use the remaining Type I error not spent at an earlier analysis, regardless of the number of events observed at the final analysis. The nominal alpha level at the final analysis will be calculated by considering the correlation between the test statistics, as determined by the actual number of EFS events at IA and FA.

If the EFS hypothesis is rejected at any analysis, the $\alpha = 0.025$ (one-sided) will be rolled over to the OS test.

Table 29 Efficacy Boundaries and Properties for EFS Analyses

Analysis[†]	Value	Efficacy
IA: 86%	Z	2.1517
N: 780	p (1-sided)	0.0157
Events: 353	~HR at bound	0.7952
Month: 48	P(Cross) if HR=1	0.0157
	P(Cross) if HR=0.7	0.8841
Final Analysis	Z	2.0422
N: 780	p (1-sided)	0.0206
Events: 410	~HR at bound	0.8172
Month: 60	P(Cross) if HR=1	0.0250
	P(Cross) if HR=0.7	0.9463

EFS=event-free survival; HR=hazard ratio; IA=interim analysis

[†] This column displays the number (Events) and percentage (%) of needed EFS events, the expected sample size (N) and the estimated months (Month) after first subject is randomized for each analysis.

p (1-sided): nominal α for group sequential testing.

~HR at bound: the approximate hazard ratio required to reach an efficacy bound.

P(Cross if HR=1): the probability of crossing a bound under the null hypothesis.

P(Cross if HR=0.7): the probability of crossing a bound under the alternative hypothesis.

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

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

Overall Survival

Overall survival will be tested only if EFS superiority is demonstrated and will be tested at $\alpha = 0.025$. Table 30 below shows the bounds and boundary properties for OS testing which were derived using a Lan-DeMets O'Brien-Fleming alpha spending function. Note that the bounds and nominal alpha levels provided in Table 30 are based on the assumption that the number of OS events at IA and FA are 220 and 268, respectively. If the actual number of events at the OS analyses differs from those specified in the table, the same minimum spending approach as used for EFS will be implemented and the bounds will be adjusted accordingly. The final OS analysis will occur at the same time as the final EFS analysis, and the final OS analysis will use the remaining Type I error not spent at an earlier analysis, regardless of the number of events observed at the final analysis.

Table 30 Efficacy Boundaries and Properties for OS Analyses

Analysis[†]	**Value**	**Efficacy**
IA: 82%	Z	2.2169
N: 780	p (1-sided)	0.0133
Events: 220	~HR at bound	0.7412
Month: 48	P(Cross) if HR=1	0.0133
	P(Cross) if HR=0.71	0.6239
Final Analysis	Z	2.0305
N: 780	p (1-sided)	0.0212
Events: 268	~HR at bound	0.78
Month: 60	P(Cross) if HR=1	0.025
	P(Cross) if HR=0.71	0.79

HR=hazard ratio; IA=interim analysis; OS=overall survival.

[†] This column displays the number (Events) and percentage (%) of needed OS events, the expected sample size (N) and the estimated months (Month) after first subject is randomized for each analysis.

p (1-sided): nominal α for group sequential testing.

~HR at bound: the approximate hazard ratio required to reach an efficacy bound.

P(Cross if HR=1): the probability of crossing a bound under the null hypothesis.

P(Cross if HR=0.71): the probability of crossing a bound under the alternative hypothesis.

8.8.2 Multiplicity Control for Safety Analyses

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

8.9 Sample Size and Power Calculations

The study will randomize approximately 780 subjects in a 1:1 ratio into the experimental arm of pembrolizumab in combination with CRT and the control arm of placebo in combination with CRT.

Power and IA calculations for EFS and OS were performed using the gsDesign R package,

Event-Free-Survival

The EFS hypothesis testing strategy was designed for α=0.025 (one-sided) and power of 94.6% to detect a HR of 0.7 with 410 EFS events at the final analysis. The sample size was estimated based on the following assumptions:

(1) true HR of 0.7;

(2) the duration of EFS in the placebo in combination with CRT group is assumed to follow a piece-wise constant hazard exponential distribution with a cumulative EFS rate of 70% at 12 months, and 40% at 36 months;

(3) an enrollment of 25 months, with accrual rates of 2 subjects per month for the first 2 months, 10 subjects per month for the next 2 months, ~24 subjects per month for the next 2 months, and ~38 subjects per month thereafter; and

(4) a 10% cumulative dropout rate at 12 months in both treatment groups.

Overall Survival

At α=0.025 (one-sided), the final OS hypothesis test yields 79% power to detect a HR of 0.71 with 268 deaths observed. The power was estimated based on the following assumptions:

(1) true HR of 0.71;

(2) the duration of OS in the placebo in combination with CRT group is assumed to follow a piece-wise constant hazard exponential distribution with a cumulative OS rate of 85% at 12 months, 65% at 36 months and 48% at 96 months;

(3) the same enrollment assumption as used for EFS; and

(4) a 3% cumulative dropout rate at 12 months in both treatment groups.

8.10 Subgroup Analyses and Effect of Baseline Factors

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 endpoint will be estimated and plotted within each category of the following classification variables:

- Geographic region (North America vs. European Union vs. Rest of the World)
- RT regimen (AFX vs. SFX)
- HPV status (Positive vs. Negative)
- ECOG Performance Score (0 vs. 1)
- Disease stage at baseline (Stage III vs. Stage IV)

- PD-L1 status (Combined Positive Score [CPS]≥1 vs. CPS<1)
- Age (<65 vs. ≥65)
- Sex (Female vs. Male)
- Race (White vs. All Others)
- Primary tumor location (Hypopharynx vs. Larynx vs. Oral cavity vs. Oropharynx)

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 subjects in a category of a subgroup variable is less than 10% of the ITT population, the subgroup analysis will not be performed for this category of the subgroup variable, and this subgroup variable will not be displayed in the forest plot. The subgroup analysis will be conducted using an unstratified Cox model.

Country-specific populations may also be analyzed per local regulatory requirements, and the primary endpoint may be estimated and plotted within each category of the above classification variables in country-specific populations.

8.11 Compliance

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

8.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in cycles. Summary statistics will be provided on extent of exposure for the ASaT population.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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 investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical supplies will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies.

Table 31 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
Pembrolizumab (MK-3475), 100 mg/4 mL	Injection	Provided centrally by the Sponsor.
Cisplatin, 1 mg/mL	Injection	Provided centrally by the Sponsor or locally by the trial site, subsidiary or designee.
		Note: Cisplatin will be provided locally in some countries by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

All supplies indicated in Table 31 will be provided per the "Source/Additional Information" column depending on local country operational requirements.

Any commercially available product not included in Table 31 will be provided by the trial site, subsidiary or designee. 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.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Study sites will receive open label pembrolizumab kits and open label cisplatin kits.

9.3 Clinical Supplies Disclosure

This trial is blinded but supplies are provided open label; therefore, an unblinded pharmacist or qualified trial site personnel will be used to blind supplies. Treatment identity (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

The emergency unblinding call center will use the treatment/randomization schedule for the trial to unblind subjects and to unmask trial treatment identity. The emergency unblinding call center should only be used in cases of emergency (see Section 7.1.7.2). In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic treatment allocation/randomization system (IVRS/IWRS) should be used in order to unblind subjects and to unmask treatment/vaccine identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. 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.

9.6 Standard Policies

Trial site personnel will have access to a central electronic treatment allocation/randomization system (IVRS/IWRS system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) 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.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, 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 subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject 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 subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 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.

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 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 (e.g., 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 Section 12.1 - MSD Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

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

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

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 as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

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

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.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, MSD, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the Protocol/CSR CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 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 subjects 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.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, 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.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

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

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. MSD will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to

the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

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12.0 APPENDICES

12.1 Code of Conduct for Clinical Trials

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

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, planning, 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 MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Input may be considered from a broad range of stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and healthcare providers to ensure operational feasibility. Trial design also includes proactive identification of critical to quality factors using a risk-based approach. Plans are then developed to assess and mitigate risks to those factors as appropriate during the trial. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD'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. Individuals involved in trial conduct receive training commensurate with their role prior to their becoming involved in 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 prespecified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

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

III. Participant Protection

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

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

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

B. Safety

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

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. 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.

During trial planning, the need for an independent Data Monitoring Committee (DMC) is assessed. DMC review of data accumulated during the conduct of the trial is integral to the well-being of trial participants.

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: 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 7.1.3.7 – 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. Subjects for Enrollment

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

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects 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 subjects on the visit designated in the trial flow chart. If delayed, present consent at next possible Subject Visit. Consent forms signed by the subject 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 subject 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 trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

4. Confidential Subject 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 subject' 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 subject 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 subject 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 utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., 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]

Subjects may withdraw their consent for Future Biomedical Research and ask that their biospecimens not be used for Future Biomedical Research. Subjects 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 subject'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 subject 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 (e.g., 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 subject'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 Subjects[3,4]

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject 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 subjects. Subjects 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 subjects 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 subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for Future Biomedical Research (i.e., only leftover samples are being retained).

The Sponsor has developed strict security, policies and procedures to address subject 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[3,4]

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/

12.3 Abbreviations

Abbreviation/Term	Definition
5-FU	5-fluorouracil
ADA	Anti-drug Antibodies
AE	Adverse Event
AFX	Accelerated Fractionation
AJCC	American Joint Committee on Cancer
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
aPTT	Activated Partial Thromboplastin Time
ASaT	All Subjects as Treated
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
AUC	Area Under the Curve, or Area under the concentration-time curve
BCG	Bacillus Calmette–Guérin
BICR	Blinded Independent Central Review
BID	Twice (two times) a Day
BSA	Body Surface Area
CBC	Complete Blood Count
CD28	Cluster of Differentiation 28
CD3ζ	CD3 zeta
CI	Confidence Interval
CNS	Central Nervous System
CPS	Combined Positive Score
CR	Complete Response
CrCl	Calculated Creatinine Clearance
CRF	Case Report Form
CRT	Chemoradiation Therapy
CRU	Clinical Research Unit
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Antigen-4
CTV	Clinical Target Volume
DAHANCA	Danish Head and Neck Cancer group
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DSMB	Date and Safety Monitoring Board
DOR	Duration of Response
ECE	Extracapsular Extension
ECG	Electrocardiogram
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
eDMC	External Data Monitoring Committee
EEA	European Economic Area
EFS	Event Free Survival
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC	European Organization for Research and Treatment of Cancer

Abbreviation/Term	Definition
EQ-5D	European Quality of Life-5 Dimension
ERC	Ethics Review Committee
ESMO	European Society for Medical Oncology
EU	European Union
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDG-PET	Fludeoxyglucose Positron Emission Tomography
FFPE	Formalin-fixed Paraffin Embedded
FNA	Fine Needle Aspirate
FSH	Follicle Stimulating Hormone
FSR	First Site Ready
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GTV	Gross Tumor Volume
GTVn	Gross Nodal Tumor Volume
GTVp	Gross Primary Tumor Volume
Gy	Gray
HBsAg	Hepatitis B surface Antigen
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
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICRU	International Commission on Radiation Units & Measurements
IFN γ	Interferon gamma
Ig	Immunoglobulin
IgG4	Immunoglobulin
IGRT	Image-Guided Radiation Therapy
IgV	Ig-variable
IHC	Immunohistochemistry
IL-2	Interleukin-2
IL-10	Interleukin-10
IMRT	Intensity Modulated Radiation Therapy
INR	International Normalized Ratio
irAE	Immune-related AEs
IRB	Institutional Review Board
ITFB	Investigator Trial File Binder
ITIM	Immunoreceptor Tyrosine-based Inhibition Motif
ITSM	Immunoreceptor Tyrosine-based Switch Motif
ITT	Intention-To-Treat
IV	Intravenous
IVD	In vitro diagnostic
IVRS	Interactive Voice Response System
IWRS	Integrated Web Response System
kg	Kilogram
JV	Kilo voltage

Abbreviation/Term	Definition
LA HNSCC	Locally Advanced Head and Neck Squamous Cell Carcinoma
LRC	Local Regional Control
LS	Least square
mAb	Monoclonal Antibody
MASCC	Multinational Association of Supportive Care in Cancer
mcL	Microliters
MDT	Multidisciplinary Team
MEL	Melanoma
mg	Milligram
mg/kg	Milligram per Kilogram
MSD ISP	Merck Sharpe & Dohme Investigator Studies Program
mL	Milliliter
MRI	Magnetic Resonance Imaging
mRNA	messenger RNA
MSI	Microsatellite instability (MSI)
MTD	Maximum Tolerated Dose
MV	Megavolt
NA or N/A	Not Applicable
NCI	National Cancer Institute
NSAID	Non-Steroidal Anti-inflammatory Drug
NSCLC	Non-Small Cell Lung Cancer
OAR	Organ(s) at Risk
ORR	Objective Response Rate
OS	Overall Survival
OTC	Over-the-counter
PBPK	Physiologically Based Pharmacokinetics
PCL	Protocol Clarification Letter
PD	Progressive Disease
PD-1	Programmed Cell Death Receptor 1
PD-L1	Programmed Cell Death Receptor Ligand 1
PD-L2	Programmed Cell Death Receptor Ligand 2
PEG	Percutaneous Gastrostomy
PET	Positron Emission Tomography
PFS	Progression Free Survival
PIN	Personal Identification Number
PK	Pharmacokinetic
PKCθ	Protein kinase C-theta
PO	Per oral
PR	Partial Response
PRO	Patient Reported Outcome
PRV	Planning Organ at Risk Volume
PS	Performance Status
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PTV	Planning Target Volume
QART	Quality Assurance in Radiotherapy
QLQ-C30	Quality of Life Questionnaire C-30
QLQ-H&N35	Quality of Life Questionnaire Head and Neck 35
QoL	Quality of Life
QW	Every Week
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks

Abbreviation/Term	Definition
R/M	Recurrent or Metastatic
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RP	Retropharyngeal
RT	Radiotherapy or Radiation Therapy
RT QA	Radiation Therapy Quality Assurance
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SFU	Survival Follow-Up
SFX	Standard Fractionation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SIB-IMRT	Simultaneous Integrated Boost Intensity Modulated Radiation Therapy
SITC	Society for Immunotherapy of Cancer
SNP	Single Nucleotide Polymorphisms
SOC	Standard of Care
sSAP	Supplemental Statistical Analysis Plan
t½	Terminal half-life
T1DM	Type 1 Diabetes
TCR	T-cell Receptor
TIL	Tumor-infiltrating Lymphocytes
TMDD	Target-mediated Drug Disposition
TNBC	Triple Negative Breast Cancer
TNFα	Tumor Necrosis Factor Alpha
TPS	Tumor Proportion Score
TRAE	Treatment Related Adverse Event
Tregs	Regulatory T-cells
TSH	Thyroid Stimulating Hormone
UICC	Union for International Cancer Control
ULN	Upper Limit of Normal
USA	United States of America
VOP	Verification of Progression
WBC	White Blood Cell
ZAP70	Zeta-chain–associated Protein Kinase

12.4 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html).

12.5 ECOG Performance Status

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

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

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

12.6 Calculation of the Glomerular Filtration Rate (GFR)

COCKCROFT AND GAULT FORMULA

For the calculation of GFR age is measured in years and weight is measured in kilograms.

If serum creatinine is measured in µmol/l, the following formula applies:

In males: $GFR[ml/min] = \frac{1.23 \times (140 - age) \times weight}{serum\ creatinine}$

In females: $GFR[ml/min] = \frac{1.05 \times (140 - age) \times weight}{serum\ creatinine}$

If serum creatinine is measured in mg/dl, the following formula applies:

In males: $GFR[ml/min] = \frac{(140 - age) \times weight}{72 \times serum\ creatinine}$

In females: $GFR[ml/min] = \frac{0.85 \times (140 - age) \times weight}{72 \times serum\ creatinine}$

12.7 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

12.8 Cisplatin Market Authorization (for sites conducting study in France only)

See website http://base-donnees-publique.medicaments.gouv.fr for the most recent version of the medicines SmPC.

12.9 Technical Note for the Piecewise Constant Hazard Exponential Survival

Given a set of time points, $0 = \tau_0 < \tau_1 < \cdots < \tau_{m-1} < \tau_m$ the piecewise constant hazard function is defined as

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

The exponential survival function is

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

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

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

12.10 Country-specific Requirements

12.10.1 France-specific Requirements

Subjects should be permanently discontinued from study treatment if any of the following AEs occur:

- Stevens-Johnson Syndrome
- Toxic-epidermal necrolysis
- Recurrent Grade 3 colitis

12.10.2 Japan-specific Requirements

Section 5.2 Trial Treatment(s)

Table 2 Trial Treatments: Intravenous solution, not provided by the Sponsor, as Placebo for MK-3475 in this protocol is not categorized as “product(s) used in the clinical trial” in Japan.

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

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 (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	