**TITLE: A Randomized, Phase II Study Evaluating Concurrent or Sequential Fixed-Dose Pembrolizumab in Combination with Cisplatin and Intensity Modulated Radiotherapy (IMRT) in Intermediate or High Risk, Previously Untreated, Locally Advanced Head and Neck Cancer**

| | |
|---|---|
| **HCC Study Number:** | 15-132 |
| **Phase:** | Randomized Phase II |
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| **Investigational Agent:** | Pembrolizumab |
| **Commercial Agent:** | Cisplatin |
| **Radiation Therapy:** | Intensity Modulated Radiotherapy (IMRT) |


**SPONSOR-INVESTIGATOR:** David Clump MD
UPMC Hillman Cancer Center
5230 Centre Avenue
1st floor Posner Tower
Pittsburgh, PA 15232
Phone: (412) 623-6720 (24 hours)

**CO-CHAIRS:**

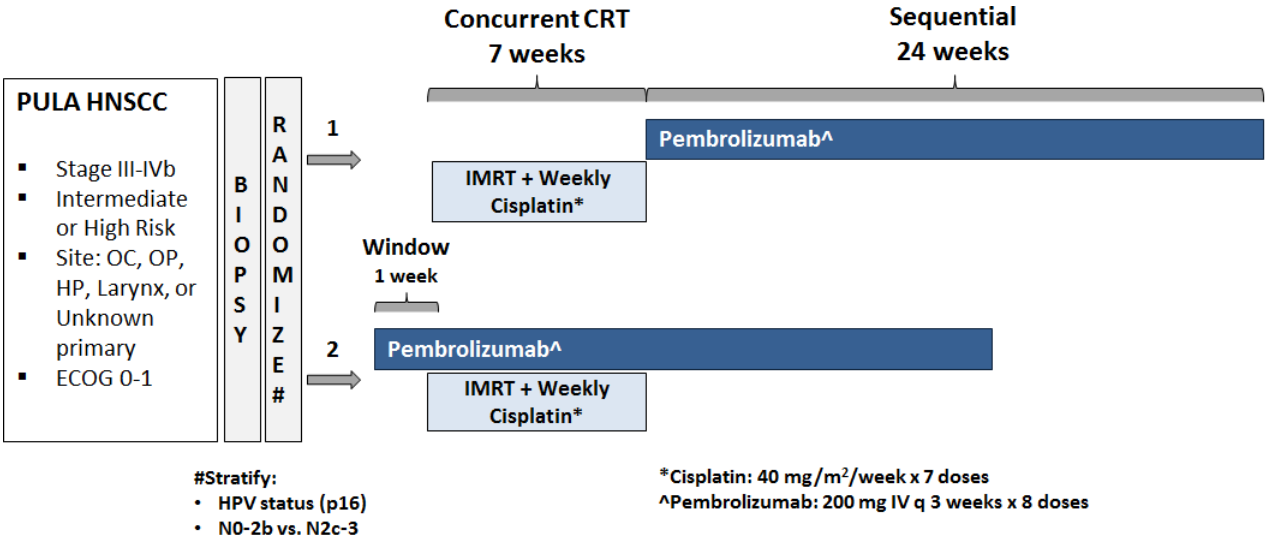
| | | |
|---|---|---|
| **Radiation Oncology:** | Jonathan J. Beitler, MD, MBA | (Emory University) |
| Medical Oncology: | Julie E. Bauman, MD | (University of Arizona) |
| **Translational Science:** | Robert Ferris, MD, PhD | (UPMC) |

**BIOSTATISTICIAN:** Daniel P. Normolle, PhD
Email: dpn7@pitt.edu



**Source(s) of Support**: Merck, Inc.

# STUDY SCHEMA



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# 1. BACKGROUND & RATIONALE

## 1.1 Disease Background

Head and neck squamous cell carcinoma (HNSCC) is the most common cancer arising in the upper aerodigestive tract. HNSCC is the sixth leading cancer worldwide with 600,000 cases annually.[1] Despite advances in multimodality therapy, 5-year overall survival (OS) is 40-60%, and has increased only incrementally in the past three decades.[2] The current standard of care for nonsurgical management of previously untreated locally advanced (PULA) HNSCC is concurrent cisplatin-radiotherapy (RT), which improved overall survival (OS), progression-free survival (PFS), and locoregional control (LRC) compared with RT alone in the landmark Intergroup 0126 trial.[3,4] Although LRC and OS are improved with concurrent cisplatin-RT, a meta-analysis indicated disappointing local and distant failure rates of 50% and 15% respectively, and an absolute survival benefit of only 6.5% compared to conventionally fractionated RT alone.[5]

### 1.1.1 Carcinogen-Induced HNSCC

The classic environmental risk factors for HNSCC are tobacco and alcohol exposure. Even when treated with cisplatin-RT, patients with carcinogen-induced PULA HNSCC have poor OS, PFS and LRC. In RTOG 0129[6] patients with human papillomavirus (HPV)(-) tumors had an absolute 25.1% reduction in OS at 3 years (57.1% vs. 82.4%) vs. patients with HPV(+) tumors, with similar reductions in PFS and LRC. Poor outcomes persist despite intensification with altered fractionation,[7] multi-drug induction,[8] or EGFR-targeted monoclonal antibodies (mAb).[9] For HPV(-) patients, new intensification approaches are a major unmet need.

### 1.1.2 HPV-Associated HNSCC

HPV(+) HNSCC is rapidly increasing in incidence.[10] In the US, two-thirds of patients with oropharynx cancer have HPV(+) tumors. HPV status and pack-years of tobacco exposure are the major determinants of OS in HNSCC, followed by nodal stage.[6] Based upon HPV status, pack-years and nodal stage, patients with HNSCC can be classified patients into three risk groups having low, intermediate, or high risk of death. This clinical risk classification has framed national clinical trial priorities in PULA HNSCC. Specifically, de-intensification strategies are being tested in patients with low-risk HPV(+) HNSCC whereas intensification strategies are the major unmet need for high-risk HPV(-) and intermediate-risk HPV(+) disease.[11,12]

## 1.2 Pembrolizumab

Pembrolizumab (formerly 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 protein 1 (PD-1) and its ligands, PD-L1 and PD-L2. Keytruda™ (Pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

Pembrolizumab was studied in a Phase Ib expansion cohort in patients with recurrent/metastatic HNSCC.[13] Preliminary clinical data were promising. Half of patients had a decrease in tumor burden and 20% met criteria for RECIST response, which was equivalently distributed between HPV(+) and HPV(-) patients. Striking activity in a heavily pre-treated HNSCC population, coupled to mechanistic insights regarding the importance of PD-1 in HNSCC immune escape, justify the investigation of pembrolizumab in PULA HNSCC.

Please refer to the pembrolizumab Investigator Brochure (IB) for descriptions of all preclinical and clinical available data.

### 1.2.1 Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades.[14] Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies.[15-19] In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2).[20,21] The structure of murine PD-1 has been resolved.[22] PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is 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 (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade.[20,23-25] The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins.[26,27] PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells.[28,29] Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells.[30] The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors[26,31-33] Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues.[26] Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL).[34] This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

### 1.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) was conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated, and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the pembrolizumab program has shown that a lower dose of pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight-based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients; 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W; 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks; 2) will maintain individual patient exposures in the exposure range established in melanoma as

associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

## 1.3 Other Protocol-Specified Drug(s) Background: Cisplatin

In PULA HNSCC, where cancer involves regional cervical lymph nodes, the cornerstone chemotherapeutic in the definitive radiotherapy setting has been cisplatin.[4,35,36] This standard of care derives from the sentinel Intergroup trial 0126, a randomized phase III trial evaluating radiation alone, concurrent cisplatin-radiation, or split course radiation with sequential administration of cisplatin-5FU.[4] The trial demonstrated a significant survival benefit for patients treated on the cisplatin-radiation arm compared to radiation alone resulting in the current, preferred standard of care for non-operative management as published in national guidelines.[37]

Cisplatin [*cis*-diamminedichloroplatinum(II)] reacts with DNA to form single base adducts, intrastrand crosslinks between 2 bases, and the uniquely lethal interstrand crosslink (ICL).[38] The considerable toxicities of cisplatin include nausea, hearing loss, nephrotoxicity, myelosuppression, and exacerbation of radiation effects such as mucositis and dysphagia.[4,39,40]

In Intergroup trial 0126, as well as the adjuvant high risk trials RTOG 95-01 and EORTC 22931, cisplatin was administered at 100 mg/m$^2$every 3 weeks for a total of three doses. High dose bolus cisplatin, as dosed in these studies, is clearly associated with greater ototoxicity, nephrotoxicity, and emetogenicity compared to daily or weekly cisplatin schedules.[41-44] Moreover, compliance with three cycles of high dose cisplatin is limited; only 64-70% of patients completed three cycles in these studies. Recognition of the importance of the cumulative dose of cisplatin, greater than or equal to 200 mg/m$^2$, rather than the dosing schedule *per se*, has resulted in increasing preference for weekly dosing schedules.[4,42-45] The RTOG now accepts cisplatin 40 mg/m$^2$/week concurrent with radiation as the reference standard of care for the adjuvant management of high risk HNSCC (RTOG 1216).

This protocol will use a cisplatin-IMRT backbone consisting of concurrent weekly cisplatin for a total of 7 doses, rather than high-dose bolus cisplatin, in order to facilitate treatment intensification with pembrolizumab. The starting cohort will utilize 40 mg/m$^2$; however if the fixed dose of pembrolizumab cannot be added to cisplatin-IMRT without dose-limiting toxicity, then the cisplatin dose will be de-escalated to 30 mg/m$^2$ which still results in a cumulative dose of 210 mg/m$^2$.

## 1.4 Study Rationale

### 1.4.1 PD-1 in HNSCC

Immunotherapy may be the “fourth modality” in HNSCC, long recognized as an immunosuppressive disease. Patients display tumor-permissive cytokine profiles, defective antigen presenting cells (APC), and quantitative and qualitative T lymphocyte deficiencies.[46-56] HNSCC tumor-infiltrating lymphocytes (TILs) are characterized by high expression of the co-inhibitory receptors CTLA-4 and PD-1, so-called “immune checkpoints.”[54,57] Following activation of the T cell receptor (TCR), PD-1 is expressed by multiple immune cells including cytotoxic T lymphocytes (CTLs), natural killer cells and dendritic cells. The PD-1 ligands,

PD-L1 and PD-L2, are expressed broadly on non-hematopoietic tissue in response to IFN-γ; PD-1 ligation protects against autoimmunity.[58] However, in the case of HNSCC, PD-1 promotes tolerance and immune escape. PD-L1 is expressed in the majority of HNSCC, and is explicitly linked to the immune-privileged, invasive front of HPV-transformed HNSCC.[15,59,60] Moreover, PD-L1 is dynamically upregulated in response to RT.

### 1.4.2 PD-1 and Radiation

Ionizing RT is understood to induce adaptive immune responses via three broad mechanisms, which could be synergistic with immunotherapy: 1) RT-induced tumor cell death releases tumor antigens (TA) for processing and presentation by APCs; 2) RT upregulates chemokines within the tumor microenvironment (TME), recruiting TILs and 3) non-lethal RT modulates the tumor phenotype, increasing expression of TA and MHC, rendering it more vulnerable to CTL killing.[61] However, RT also induces local immune suppression by upregulation of PD-L1 on both tumor and myeloid-derived suppressor cells (MDSC), reducing the adaptive response and theoretically facilitating future relapse. In two preclinical models, concurrent PD-L1 blockade and RT were synergistic in controlling tumor growth, and generated prolonged protective T cell immunity as demonstrated by subsequent abscopal effect.[62]

## 2. STUDY OBJECTIVES

### 2.1 Primary

**To evaluate two schedules of fixed-dose pembrolizumab (concurrent vs. sequential) added to standard, concurrent cisplatin-IMRT in patients with PULA HNSCC, in order to recommend the schedule to be tested in a subsequent definitive, randomized study.**

(please see Section 9.2 for Statistical Methods).

### 2.2 Secondary

Secondary objectives for this study include:

- To evaluate the toxicity of two sequences of the combination of pembrolizumab and concurrent cisplatin-IMRT in patients with PULA HNSCC.

## 3. PATIENT SELECTION

### 3.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

- Patients must have histologically-confirmed head and neck squamous cell carcinoma with no evidence of distant metastasis. The primary site may be the oral cavity, oropharynx, larynx, or hypopharynx. Patients with squamous cell carcinoma of unknown primary, metastatic to cervical lymph nodes, are permitted to enroll.
- Patients must have high risk or intermediate risk disease, defined below. Staging evaluation should be determined by imaging studies and complete head and neck exam in accordance with the American Joint committee on Cancer Staging Manual, 7$^{th}$ edition.
    - High risk patient must meet one of the following criteria:
        - Surgically unresectable oral cavity. Patients who are technically resectable but refuse surgery due to morbidity (eg. total glossectomy) are also eligible. Medically inoperable patients are not eligible.
        - Larynx: T4 any N; T2-3 and ≥ N2a.

- Hypopharynx: T1-2N1-3 or T3-4N0-3.
- Oropharynx: p16(-) AND T3-4 or ≥ N2a.
- Unknown primary: p16(-) AND ≥ N2a.

- Intermediate risk patients must meet one of the following criteria:
    - Oropharynx: p16(+) AND one of the following
        - T3 or ≥ N2a AND ≥ 10 pack-years tobacco exposure (see Tobacco Assessment Form, Appendix A).
        - T4 or N3 disease irrespective of tobacco exposure.
    - Unknown primary: p16(+) AND one of the following
        - ≥ N2a AND ≥ 10 pack-years tobacco exposure.
        - N3 disease irrespective of tobacco exposure.

  **Note: for patients with oropharyngeal or unknown primary tumors, p16 status must be known, and can be performed at the local site. p16-positive disease is defined as ≥70% of tumor cells demonstrating diffuse nuclear and cytoplasmic staining by p16 immunohistochemistry (IHC). A positive test for HPV-16 by in-situ hybridization (ISH), if this is the local site preference for assessing HPV status, may substitute for p16 IHC testing. p16 staining is not required for non-oropharyngeal sites.**

- Patients must be untreated with curative-intent surgery for current diagnosis of Stage III, IVa, or IVb disease. Diagnostic biopsy of primary tumor and/or nodal sites is permitted.
    - Diagnostic simple tonsillectomy is permitted, provided patient has RECIST-measurable nodal disease.
    - Patients with a second HNSCC primary tumor are eligible for this study, provided more than 2 years have elapsed since the first diagnosis of HNSCC, the original tumor was managed with surgery only (no adjuvant chemotherapy or radiotherapy), and has not recurred.
- Patients with simultaneous primaries or bilateral tumors are excluded, with the exception of patients with bilateral tonsil cancers or patients with T1-2, N0, M0 differentiated thyroid carcinoma (resected or management deferred), who are eligible.
- No prior systemic (chemotherapy or biologic/molecular targeted therapy) or radiation treatment for head and neck cancer.
    - Patients may have received chemotherapy or radiation for a previous, curatively treated non-HNSCC malignancy, provided at least 2 years have elapsed.
    - Patients must be untreated with radiation above the clavicles.
- Patients with a history of curatively-treated non-HNSCC malignancy must be disease-free for at least 2 years except for excised and cured: carcinoma-in-situ of breast or cervix; non-melanomatous skin cancer; T1-2, N0, M0 resected differentiated thyroid carcinoma; superficial bladder cancer; T1a or T1b prostate cancer comprising < 5% of resected tissue with normal prostate specific antigen (PSA) since resection.

- Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1 (See Appendix B)
- Age ≥ 18
- Patients must have measurable disease according to RECIST 1.1 (See Section 6.1)
- Patients must demonstrate adequate organ function as defined in; all screening labs should be performed within 14 days of treatment initiation.

**Table 1. Adequate Organ Function Laboratory Values**

| System | Laboratory Value |
|---|---|
| **Hematological** | |
| Absolute neutrophil count (ANC) | ≥1,500 /mm$^3$ |
| Platelets | ≥100,000 / mm$^3$ |
| **Renal** | |
| Serum creatinine **OR**<br>Measured or calculated[a] creatinine clearance<br>(GFR can also be used in place of creatinine or CrCl) | ≤1.5 X upper limit of normal (ULN) **OR**<br><br>Creatinine clearance ≥60 mL/min (for subject with creatinine levels > 1.5 X institutional ULN) determined by 24-hour collection or estimated by Cockcroft-Gault formula:<br><br>**Calculated creatinine clearance = [(140-age) X (actual body weight in kg) X (0.85 if female)]/(72 X serum creatinine)** |
| **Hepatic** | |
| Serum total bilirubin | ≤ 1.5 X ULN **OR**<br>Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN |
| AST (SGOT) and ALT (SGPT) | ≤ 2.5 X ULN |
| **Coagulation** | |
| International Normalized Ratio (INR) or Prothrombin Time (PT)<br><br>Activated Partial Thromboplastin Time (aPTT) | ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants<br>≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants |

- Written informed consent must be obtained from all patients prior to study registration. Patients should have the ability to understand and the willingness to sign a written informed consent document.
- If a woman of childbearing potential, documentation of negative pregnancy.
- Within 14 days prior to first dose (see section 8.1.1). Sexually active patients must agree to use adequate contraceptive measures, while on study and for 30 days after the last dose of study drug. All fertile female subjects (and their partners) must agree to use a highly effective method of contraception. Effective birth control includes (a) intrauterine device (IUD) plus one barrier method; or (b) 2 barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm). Should a woman become pregnant or suspect she is pregnant while in this study, she should inform her treating physician immediately.

## 3.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

- Nasopharyngeal primary site.
- Current participation in or previous participation in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of study treatment.

- History of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the investigational agent.
- Distant metastatic disease including CNS or leptomeningeal metastases is not allowed.
- History 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.
- Received prior monoclonal antibody (for cancer) within 4 weeks prior to study Day 1 or who has not recovered (i.e. ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
- History of second malignancy within 2 years prior to Study Day 1 (except for excised and cured non-melanoma skin cancer, carcinoma in situ of breast or cervix, superficial bladder cancer, or T1a or T1b prostate cancer comprising < 5% of resected tissue with normal prostate specific antigen (PSA) since resection).
- Active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with known hypothyroidism stable on hormone replacement, subclinical hypothyroidism, or Sjogren's syndrome will not be excluded from the study.
- Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note: HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the cisplatin and IMRT involved in this protocol may be significantly immunosuppressive. Patients with known HIV, CD4 counts ≥ 250/μL, and undetectable viral loads who are stable on an antiretroviral regimen may be included.
- Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
- Received a live vaccine within 30 days prior to the first dose of trial treatment.
- Received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
- Significant pulmonary disease, including pulmonary hypertension, interstitial lung disease, or active, non-infectious pneumonitis.
- History or current evidence of any other medical or psychiatric 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.
- Peripheral neuropathy ≥ Grade 2
- Significant cardiovascular disease, including:
    - Cardiac failure New York Heart Association (NYHA) class III or IV.
    - Myocardial infarction, severe or unstable angina within 6 months prior to Study Day 1.
    - History of serious arrhythmia (i.e., ventricular tachycardia, or ventricular fibrillation).

- Ventricular cardiac arrhythmias requiring anti-arrhythmic medications.
- Known left ventricular ejection fraction (LVEF) ≤ 50%.

- Significant thrombotic or embolic events within 3 months prior to Study Day 1. Significant thrombotic or embolic events include but are not limited to stroke or transient ischemic attack (TIA). Catheter-related thrombosis is not a cause for exclusion. Diagnosis of deep vein thrombosis or pulmonary embolism is allowed if the patient is clinically stable and has completed or is on stable anti-coagulation therapy.
- Major surgery within 6 weeks prior to Study Day 1 (subjects must have completely recovered from any previous surgery prior to Study Day 1). Biopsy, diagnostic tonsillectomy, airway tumor debulking or excisional lymph node biopsy do not constitute major surgery.
- Active infection requiring antibiotics or antifungals within 7 days prior to first dose of study drug.
- Significant electrolyte imbalance prior to enrollment (note that patients may be supplemented to achieve acceptable electrolyte values):
  - Hypomagnesemia < 1.2 mg/dL or 0.5 mmol/L.
  - Hypokalemia < 3.0 mmol/L.
- Women must not be pregnant or breastfeeding because chemotherapy and/or pembrolizumab may be harmful to the fetus or the nursing infant. Pregnant women are excluded from this study because chemotherapy and/or pembrolizumab have the potential for teratogenic or abortifacient effects.

## 4. PATIENT REGISTRATION/RANDOMIZATION

Note: All patients can be registered following eligibility confirmation by calling the coordinating center study liaison, Carrie Muniz, RN, BSN:

5150 Centre Avenue
Suite 301
Pittsburgh, PA 15232
Phone: (412) 623-6121
Fax: (412) 648-6650
E-mail: munizca@upmc.edu

For questions regarding the eligibility of subjects, please contact the study doctor, David Clump, MD, at (412) 623-6720.

Registration will require the following information: 1) your name, telephone and email; 2) protocol name and number; 3) date treatment begins; 4) subject name; 5) date of birth; 6) subject hospital medical record number; 7) primary study physician; 8) primary treatment institution; 9) confirmation of eligibility; 10) copies of the informed consent signature page and 11) verification that the informed consent was signed.

Randomization will occur at the UPCI Biostatistics Core once consent and eligibility are verified.

# 5. TREATMENT PLAN

Arm 1 (Table 2): Pembrolizumab will be initiated 2 weeks after the completion of cisplatin-IMRT (week 9 of protocol treatment) and administered at the fixed dose of 200 mg IV q 3 weeks (+/- 3 days) for a total of 24 weeks (8 doses; 6 months). NOTE: Per discretion of the treating investigator, the week 9 dose of pembrolizumab may be delayed up to 3 weeks for recovery of acute toxicities from chemoradiotherapy. This dose would be considered delayed, and all subsequent doses would be administered at a q 3 week interval (+/- 3 days) from first pembrolizumab dose.

Arm 2 (Table 3): Pembrolizumab will be initiated 1 week prior to cisplatin-IMRT (the "window") at the dose of 200 mg IV q 3 weeks (+/- 3 days). Pembrolizumab will be continued concurrently through cisplatin-IMRT (weeks 3, 6), and continued for a 15 week maintenance period after completion of cisplatin-IMRT for a total pembrolizumab treatment period of 24 weeks (8 doses; 6 months). NOTE: Per discretion of the treating investigator, the week 9 dose of pembrolizumab may be delayed up to 3 weeks for recovery of acute toxicities from chemoradiotherapy. This dose would be considered delayed, and all subsequent doses would be administered at a q 3 week interval (+/- 3 days) until completion.

**Table 2. Arm 1 Treatment Plan**

| ARM 1 | Week of Treatment | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 9 | 12 | 15 | 18 | 21 | 24 | 25 | 30 |
| IMRT | X | X | X | X | X | X | X | | | | | | | | |
| Cisplatin | X | X | X | X | X | X | X | | | | | | | | |
| Pembrolizumab | | | | | | | | X | X | X | X | X | X | X | X |

**Table 3. Arm 2 Treatment Plan**

| ARM 2 | Week of Treatment | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | -1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 9 | 12 | 15 | 18 | 21 |
| IMRT | | X | X | X | X | X | X | X | | | | | |
| Cisplatin | | X | X | X | X | X | X | X | | | | | |
| Pembrolizumab | X | | | X | | | X | | X | X | X | X | X |

## 5.1 Study Drug Administration: Pembrolizumab

### 5.1.1 Route of Administration

Pembrolizumab will be administered as an IV infusion.

### 5.1.2 Doses to be Administered

The dose of pembrolizumab will be 200 mg (fixed dose) IV every 3 weeks (+/- 3 days), beginning on week 9 of treatment (Arm 1) or beginning one week (week -1) prior to concurrent cisplatin-IMRT (in Arm 2).

### 5.1.3 Dosing Schedule

Subjects will receive pembrolizumab once every 3 weeks (+/- 3 days) in an IV infusion over 30 minutes.

Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

### 5.1.4 Order of Administration

When cisplatin and pembrolizumab are administered on the same day in Arm 2, pembrolizumab should follow cisplatin. Pembrolizumab may be given either before or after the radiation therapy fraction that is given the same day.

### 5.1.5 Prohibited Concomitant Medications

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

- Colony stimulating factors, including G-CSF, pegylated G-CSF, and erythropoietin analogs.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Radiation not specified in this protocol.
- Investigational agents other than pembrolizumab.
- 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.
- Glucocorticoids for any purpose other than the following two clinical situations:
    - To control cisplatin-related nausea, if viewed as absolutely necessary for symptom control by the treating medical oncologist. NOTE: every effort will be made to minimize glucocorticoid administration either as premedication or as prophylaxis/treatment of delayed nausea from cisplatin.
    - To modulate symptoms from an event of clinical interest of suspected immunologic etiology.

Subjects who, in the assessment of the treating 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.

There are no prohibited therapies during the Post-Treatment or Follow-up phases of this trial.

## 5.2 Drug Administration – Cisplatin

### 5.2.1 Route of Administration

Cisplatin will be administered as an IV infusion.

### 5.2.2 Doses to be Administered

The starting dose of cisplatin will be 40 mg/m$^2$ weekly (+/- 3 days), beginning concurrent with IMRT during week 1 of study treatment in both Arms (see Tables 2 and 3). The actual body weight will be used for all patients. There should be no dose modifications because of obesity.

### 5.2.3 Dosing Schedule

Patients will receive cisplatin once weekly as an IV infusion over 60 minutes, for a total of 7 doses. Cisplatin should be administered on Monday, Tuesday, or Wednesday of each treatment week and may be given either before or after the radiation therapy fraction that is given on the same day. When cisplatin and pembrolizumab are administered on the same day, pembrolizumab should follow cisplatin.

### 5.2.4 Concomitant Medications during Cisplatin Infusion

#### 5.2.4.1 Nausea

Cisplatin, 30-40 mg/m$^2$, is a moderately emetogenic drug. For acute nausea and vomiting, premedication should include a 5-HT3 antagonist, such as granisetron 1 mg iv; ondansetron, up to 16 mg iv; or palonosetron, 0.25 mg iv. Palonosetron has a longer half-life (40h) than the first generation 5HT3 antagonists. NOTE: The use of a corticosteroid premedication, such as dexamethasone 10 mg IV, is typically combined with a 5-HT3 antagonist when administering weekly cisplatin. In this protocol, omitting scheduled corticosteroid premedication, due to the immunosuppressive properties, is strongly encouraged on both study arms. However, if necessary in the judgment of the treating investigator, a corticosteroid may be administered as a premedication for acute nausea/vomiting. Fosaprepitant may be administered in accordance with institutional guidelines or investigator judgment.

Breakthrough nausea and vomiting may be managed at the discretion of the treating investigator. Delayed nausea and vomiting (greater than 24 hours after chemotherapy administration) may be managed per investigator discretion, including use of the following potential nausea regimens: oral metoclopramide 10 mg qid x 2-4 days; prochlorperazine 10 mg qid x 2-4 days; a 5HT3 antagonist (e.g. granisetron, ondansetron) may also be given for up to 3 days (only if palonosetron was not given prior to chemotherapy). Aprepitant may also be used for delayed nausea. NOTE: Although dexamethasone and other corticosteroids are discouraged for delayed cisplatin-induced nausea in this protocol, corticosteroids may be used if viewed as necessary by the treating investigator (e.g. 8 mg bid for 2 days, followed by 4 mg bid for 2 days).

#### 5.2.4.2 Hydration and Electrolyte Support

Patients must receive vigorous hydration and diuresis. Recommendations are to administer cisplatin, 40 mg/m$^2$, in NS 1000 ml. Additional IV fluid, potassium chloride, and/or magnesium sulfate may be administered at the discretion of the medical oncologist. Mannitol may be administered at the discretion of the medical oncologist.

## 5.3 Dose Modifications

### 5.3.1 Pembrolizumab Dose Modifications

Retreatment criteria for pembrolizumab and cisplatin are independent (retreatment criteria for cisplatin are specified in section 5.3.2 below). There are no dose reductions for pembrolizumab. If the subject meets retreatment criteria, the full dose of 200 mg will be administered. If subjects do not meet retreatment criteria, then the dose of pembrolizumab will be SKIPPED. The sole exception to this rule is the first dose of pembrolizumab following completion of chemoradiotherapy, on both Arms 1 and 2. Although scheduled for

Week 10 of protocol treatment, the first post-chemoradiotherapy dose of pembrolizumab may be DELAYED up to 3 weeks to allow for recovery from acute toxicities, in accordance with the treating investigator's judgment. In the case of such delay, the following three doses of pembrolizumab will then be scheduled every 3 weeks (+/- 3 days) from the first post-chemoradiotherapy dose.

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

Note: if after the evaluation the event is determined not to be related to pembrolizumab, the investigator is instructed to follow the Events of Clinical Interest (ECI) reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Please see section 12.4.2 for ECI reporting guidance.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

**Table 4. Pembrolizumab Dose Modification Guidelines for Drug-Related Adverse Events**

| Toxicity | Hold Pembrolizumab For NCI CTCAE Grade | Timing for Restarting Treatment | Discontinue Pembrolizumab Permanently |
|---|---|---|---|
| Out-of-field Rash (skin rash ***outside*** of the radiation field) | 3 | Toxicity resolves to Grade 0-1 and the patient has tapered off of or did not require systemic corticosteroids. (Ongoing management with topical steroids is acceptable.) | Toxicity does not resolve within 12 weeks of last dose or inability to taper off of corticosteroids within 12 weeks. |
| In-field radiation dermatitis (skin rash ***within*** the radiation field) – Arm 2 | 4[a] | Toxicity resolves to Grade 3 or less.<br>NOTE: systemic and topical steroids should be avoided in the case of radiation dermatitis that is restricted to in-field. | Toxicity does not resolve to Grade 3 or better within 6 weeks of completing IMRT |
| Diarrhea/Colitis | 2-3 | Toxicity resolves to Grade 0-1 and the patient has successfully tapered off of corticosteroids. | Toxicity does not resolve within 12 weeks of last dose or inability to taper off of corticosteroids within 12 weeks. |
| | 4 | Permanently discontinue | Permanently discontinue |
| AST, ALT, or Increased Bilirubin | 2 | Toxicity resolves to Grade 0-1 and the patient has tapered off of corticosteroids. | Toxicity does not resolve within 12 weeks of last dose. |
| | 3-4 | Permanently discontinue | Permanently discontinue |

| Toxicity | Hold Pembrolizumab For NCI CTCAE Grade | Timing for Restarting Treatment | Discontinue Pembrolizumab Permanently |
|---|---|---|---|
| Type 1 diabetes mellitus (if new onset) or Hyperglycemia | T1DM or 3-4 | Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure. | Resume pembrolizumab when patients are clinically and metabolically stable. |
| Hypophysitis | 2-3 | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose or inability to taper corticosteroids to a dose of prednisone 10 mg or less within 12 weeks. |
| | 4 | Permanently discontinue | Permanently discontinue |
| Hyperthyroidism | 3 | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose or inability to taper off corticosteroids within 12 weeks. |
| | 4 | Permanently discontinue | Permanently discontinue |
| Hypothyroidism | 2-4 | Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted | Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted. |
| Infusion Reaction | 3-4 | Permanently discontinue | Permanently discontinue |
| Pneumonitis | 2 | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose or inability taper off corticosteroid within 12 weeks. |
| | 3-4 | Permanently discontinue | Permanently discontinue |
| Renal Failure or Nephritis[b] – Serum/Whole Creatinine | 2[c] | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose or inability to taper off corticosteroid within 12 weeks. |
| | 3-4 | Permanently discontinue | Permanently discontinue |
| All Other Drug-Related Toxicity[d] | 3 or Severe | Toxicity resolves to Grade 0-1 | Toxicity does not resolve within 12 weeks of last dose or inability taper off of corticosteroids within 12 weeks. |
| | 4 | Permanently discontinue | Permanently discontinue |

**Note: Permanently discontinue pembrolizumab for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.**

[a] Per investigator discretion, pembrolizumab may be held for grade 3 in-field radiation dermatitis. If pembrolizumab is held for grade 3 in-field radiation dermatitis, no specific grade of resolution is required to restart pembrolizumab; restart would also be per investigator discretion.

[b] NOTE: Dose modification of cisplatin in the setting of renal insufficiency is addressed separately in Section 5.3.2.

[c] NOTE: if event is considered ***clinically unrelated or unlikely to be related to pembrolizumab***, and an alternate clinical explanation is likely, probable, or definite in the judgment of the investigator (example, attributable to cisplatin and/or prerenal azotemia in the setting of nausea, and responding to hydration), then corticosteroids may be omitted and pembrolizumab may be administered.

[d] Patients with intolerable or persistent Grade 2 drug-related AE may hold pembrolizumab at physician discretion. Permanently discontinue pembrolizumab for persistent Grade 2 adverse reactions for which treatment with study drug has been held, and that do not recover to Grade 0-1 within 12 weeks of the last dose of pembrolizumab. Note: Pembrolizumab does **not** need to be held for grade 3 dysphagia, grade 3 pain, grade 3 weight loss, or grade 3 fatigue, which are expected toxicities for chemoradiation of HNSCC and will be managed aggressively by treating investigators per standards of care.

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/Colitis**:
  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids (or to administer liberal quantities of clear fluids via PEG tube if present). If sufficient oral of PEG-tube fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
    - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
    - For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA):**

    - For **T1DM** or **Grade 3 – 4** Hyperglycemia:
        - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
        - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:

    - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
    - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. NOTE: Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:
  Thyroid disorders can occur at any time during treatment with pembrolizumab. Of note, patients with HNSCC undergoing cisplatin-IMRT may experience subclinical mild hyperthyroidism or euthyroid sick syndrome during IMRT, and commonly develop late hypothyroidism as a consequence of radiation dose to the thyroid. Monitor patients for changes in thyroid function (TSH and free T4 every 3 weeks on Arms 1 and 2, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. No intervention is required for Grade 1 hyperthyroidism or hypothyroidism events.

    - **Grade 2** hyperthyroidism events:
        - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - **Grade 3-4** hyperthyroidism events:
        - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Grade 2-4** hypothyroidism
  - Hypothyroidism is a common consequence of chemoradiotherapy for HNSCC, and is likely permanent. In Grade 2-4 hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.

- **Hepatic**:

  - For **Grade 2** events, monitor liver function tests weekly until returned to baseline values
    - Treat with IV or oral corticosteroids.
  - For **Grade 3-4** events, hospitalization is indicated. Treat with intravenous corticosteroids for 24 to 48 hours. Monitor liver function tests frequently.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal Failure or Nephritis**:
  Mild to moderate renal insufficiency can occur in the context of cisplatin chemotherapy. Dose modification of cisplatin in the setting of renal insufficiency is addressed separately in Section 5.3.2.

  - For **Grade 2** events at least possibly related to pembrolizumab, hold pembrolizumab and treat with vigorous hydration and oral corticosteroids. Monitor renal function weekly until returned to baseline values. NOTE: if event is considered ***clinically unrelated or unlikely to be related to pembrolizumab***, and an alternate clinical explanation is likely, probable, or definite in the judgment of the investigator (example, attributable to cisplatin and/or prerenal azotemia in the setting of nausea, and responding to hydration), then corticosteroids may be omitted and pembrolizumab may be administered.
  - For **Grade 3-4** events, hospitalization is indicated. Treat with vigorous hydration and IV corticosteroids for 24 to 48 hours. Monitor renal function frequently. Consultation with nephrology is recommended.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

**Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

**Table 5. Infusion Reaction Treatment Guidelines**

| NCI CTCAE Grade | Treatment | Premedication at subsequent dosing |
|---|---|---|
| Grade 1<br>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<br>Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs | **Stop Infusion and monitor symptoms.**<br>Additional appropriate medical therapy may include but is not limited to:<br>IV fluids<br>Antihistamines<br>NSAIDS<br>Acetaminophen<br>Narcotics<br>Increase monitoring of vital signs as medically indicated until the subject is | Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with:<br><br>Diphenhydramine 50 mg po (or equivalent dose of antihistamine). |

| NCI CTCAE Grade | Treatment | Premedication at subsequent dosing |
|---|---|---|
| | deemed medically stable in the opinion of the investigator.<br>If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., 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.<br>**Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further pembrolizumab administration.** | Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic). |
| Grades 3 or 4<br>Grade 3:<br>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)<br>Grade 4:<br>Life-threatening; pressor or ventilatory support indicated | **Stop Infusion.**<br>Additional appropriate medical therapy may include but is not limited to:<br>IV fluids<br>Antihistamines<br>NSAIDS<br>Acetaminophen<br>Narcotics<br>Oxygen<br>Pressors<br>Corticosteroids<br>Epinephrine<br><br>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.<br>Hospitalization may be indicated.<br>**Subject is permanently discontinued from further pembrolizumab administration.** | **No subsequent dosing of pembrolizumab** |
| Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. | | |

### 5.3.2 Cisplatin Dose Modifications

There is one level of dose reduction for cisplatin (dose level -1): when dose reduction is required, cisplatin will be reduced to 30 mg/m$^2$/week. There is no dose level below 30 mg/m$^2$. Retreatment criteria for pembrolizumab and cisplatin are independent. Dose modifications for cisplatin are specified for hematologic and non-hematologic toxicity in Tables 6 and 7 below.

Table 6. Cisplatin Dose Modifications for Hematologic Toxicity

| **NCI CTCAE Toxicity Grade (CTCAE v. 4)** | **Cisplatin Dose[c,d] at Start of Subsequent Cycles of Therapy** |
|---|---|
| **Neutropenia** | |
| **1** (1500-1999/$mm^3$) | Maintain cisplatin dose level |
| **2** (1000-1499/$mm^3$) | Maintain cisplatin dose level |
| **3** (500-999/$mm^3$) | Hold cisplatin dose for the week; check CBCD weekly. Resume cisplatin at dose level -1 (30 mg/$m^2$/week) when neutropenia recovers to Grade 2 or better. |
| **4** (<500/$mm^3$) | Hold cisplatin dose for the week; check CBCD weekly. Resume cisplatin at dose level -1 (30 mg/$m^2$/week) when neutropenia recovers to Grade 2 or better. |
| **Second incident, grade 3-4 neutropenia** | Hold cisplatin and recheck CBCD weekly. Resume cisplatin at 30 mg/$m^2$/week when neutropenia reaches Grade 2 or better. |
| **Neutropenic Fever[e]** | Hold cisplatin and initiate standard treatment. Resume cisplatin at 30 mg/$m^2$/week when neutropenia has recovered to Grade 2 or better, neutropenic fever has resolved, and patient is stable. |
| **Thrombocytopenia** | |
| **1** (75,000/$mm^3$-LLN) | Maintain cisplatin dose level |
| **2** (50,000- 74,999/$mm^3$) | Hold cisplatin dose for the week; check CBCD weekly. Resume cisplatin at dose level -1 (30 mg/$m^2$/week) when thrombocytopenia recovers to Grade 1 or better. |
| **3** (25,000- 49,999/$mm^3$) | Hold cisplatin dose for the week; check CBCD weekly. Resume cisplatin at dose level -1 (30 mg/$m^2$/week) when thrombocytopenia recovers to Grade 1 or better. |
| **4** <25,000/$mm^3$) | Hold cisplatin dose for the week; check CBCD weekly. Resume cisplatin at dose level -1 (30 mg/$m^2$/week) when thrombocytopenia recovers to Grade 1 or better. |
| **Second incident, grade 2-4 thrombocytopenia** | Hold cisplatin and recheck CBCD weekly. Resume cisplatin at 30 mg/$m^2$/week when thrombocytopenia reaches Grade 1 or better. |

Table 7. Cisplatin Dose Modifications for Non-hematologic Toxicity

| **NCI CTCAE Toxicity[a] Grade (CTCAE v. 4)** | **Cisplatin Dose[b]** |
|---|---|
| **Renal-serum Creatinine** | |
| ≤ Grade 1 (ULN-1.5 x ULN) | Maintain cisplatin dose level |
| Grade 2 (> 1.5-3.0 x ULN) | Hold cisplatin. Check serum creatinine weekly. Resume cisplatin at dose level -1 (30 mg/$m^2$/week) when recovered to Grade 1 or baseline. |
| ≥ Grade 3 (>3.0-6.0 x ULN)[c] | Discontinue cisplatin. Per investigator discretion, the patient may be changed to carboplatin AUC 2 weekly. |
| **Fatigue** | |
| Grade 3 | Decrease cisplatin to dose level -1 (30 mg/$m^2$/week) |
| **Nausea/Vomiting** | |
| ≤ Grade 2 with maximal medical management | Maintain dose level |
| ≥ Grade 3 with maximal medical management | Hold cisplatin until ≤ grade 2, then resume cisplatin at dose level -1 (30 mg/$m^2$/week) |
| **Other non-hematologic Toxicities[d]** | |

| | |
|---|---|
| **Neuropathy**<br>Grade 2<br>Grade 3-4 | <br>Decrease cisplatin to dose level -1 (30 mg/m$^2$/week)<br>Discontinue cisplatin. Per investigator discretion, the patient may be changed to carboplatin AUC 2 weekly. |
| **Ototoxicity**<br>Grade 2<br>Grade 3-4 | <br>Decrease cisplatin to dose level -1 (30 mg/m$^2$/week)<br>Discontinue cisplatin |
| **Other:** Mucositis in RT field<br>Grade 0-3<br>Grade 4 | <br>Maintain cisplatin dose level<br>Hold cisplatin until ≤ grade 3, then resume at dose level -1 (30 mg/m$^2$/week) |
| **Rash**, in RT field (inclusive of radiation dermatitis)<br>Grade 2-3<br>Grade 4 | <br><br>Maintain dose level[d]<br>Hold cisplatin until ≤ grade 3, then resume at dose level -1 (30 mg/m$^2$/week) |
| **Rash**, out of RT field<br>Grade 1-4 | <br>Maintain cisplatin dose level |
| Grade 3-4/Other[e] | Hold cisplatin until baseline or ≤ grade 1; per investigator judgment,may resume cisplatin at dose level -1. Note exceptions in footnote.[f] |

[a]For CTCAE Grade ≤ 2 non-hematologic toxicity not described above, attributed to cisplatin, maintain dose level of cisplatin.
[b]Dose levels are relative to the previous dose. Dose reductions of cisplatin below the –1 dose level will not be allowed. For a second incident of non-hematologic toxicity of sufficient severity to requires dose modification, hold cisplatin until toxicity resolves to Grade 1 or baseline, then resume at 30 mg/m$^2$/week.
cIf Grade ≥ 3 nephrotoxicity occurs,
[d]Dose modification of cisplatin is not required in the setting of asymptomatic electrolyte abnormalities. For depressed K or Mg, administer replacement therapy per local standard. Cisplatin may continue at full dose, at the discretion of the treating physician.
[d]Per investigator discretion, cisplatin may be dose-reduced to dose level -1 or held for grade 3 radiation dermatitis.
[e] For CTCAE Grade 3-4 non-hematologic toxicity not described above, attributed to cisplatin, hold cisplatin until baseline or ≤ Grade 1. Per investigator judgment, may resume cisplatin at dose level -1.
[f] Cisplatin does **not** need to be held or dose-reduced for grade 3 dysphagia, grade 3 pain, grade 3 weight loss, or grade 3 fatigue, which are expected toxicities for chemoradiation of HNSCC and will be managed aggressively by treating investigators per standards of care.

If ototoxicity or nephrotoxicity occurs, treatment can be changed to carboplatin with AUC (area under curve) of 2 for remainder of concurrent radiotherapy.

## 5.4 Intensity Modulated Radiotherapy (IMRT)

### 5.4.1 Dose specifications

IMRT will be delivered in 35 fractions over 7 weeks (five fractions per non-holiday week) in one plan (SIB). Concomitant boost using separate IMRT plans is not allowed.

Missed treatments due to holidays or logistic reasons can be compensated for by delivering an additional BID treatment during the week, OR treating on the Saturday or Sunday of that week, OR adding to the end of treatment.

### 5.4.2 Immobilization and Simulation

Patients must have an immobilization device (e.g. Aquaplast mask) made prior to treatment planning CT scan. Use of an immobilizing mouthpiece is strongly encouraged for all patients, especially those with cancers of the oral cavity and oropharynx.

The treatment planning CT scan should be performed with IV contrast so that the major vessels of the neck are easily visualized. The treatment planning CT scan must be performed with the immobilization device and in the treatment position. Slice thickness should be 0.3 cm or thinner.

### 5.4.3 Target Delineation

The Gross Tumor Volume (GTV) is defined as all known gross disease determined from CT, PET/CT, clinical information, endoscopic findings and/or potentially MRI.

The Clinical Target Volume (CTV) is defined as the GTV plus areas considered to contain potential microscopic disease, delineated by the treating physician. The margin between each GTV and its CTV will typically be a minimum of 0.5 cm except in those areas where the GTV is immediately adjacent to structures known to be uninvolved such as bone and adjacent muscle. In this instance, the CTV should be modified to exclude structures that serve as a boundary that prevents the natural spread of disease (bone, muscle, etc).

The Planning Target Volume (PTV) will provide a margin around each CTV (i.e. both the primary tumor and the lymph nodes containing clinical or radiographic evidence of metastases) to compensate for the variation of treatment set up and internal organ motion. Studies should be implemented by each institution to define the appropriate magnitude of the uncertainty components of the PTV; however, an unedited expansion of 0.3 - 0.5 cm is recommended.

In general, the PTV should not go outside of the skin surface; if it does exceed the skin surface, the application of bolus material over this portion of the PTV may be considered if it is judged clinically that the skin is at risk but is generally not recommended.

For those institutions that are using daily IGRT for margin reduction, the minimum CTV-to-PTV expansion is 3.0 mm (a larger expansion may be necessary for a target volume subject to significant intra-fraction variability, such as the non-immobilized oral tongue). In general, the CTV-to-PTV expansion (with IGRT) should not exceed 5 mm.

The primary tumor and involved nodes (CTV1) will typically consist of a 0.5 - 1.5 cm expansion of the gross tumor volume (GTV) to cover potential local invasion and will be prescribed 2 Gy/fraction, total 70 Gy (see Section 5.4.8. for details of prescription for PTV1).

High-risk sub-clinical disease sites, which include possible local subclinical infiltration at the primary site (primary site CTV2) and first echelon nodes, which are not clinically or radiographically involved (nodal CTV2), should be expanded by 3 - 5 mm to create PTV2. PTV2 should receive a total dose of 60 Gy/35 fractions.

Lower-risk targets (PTV3) (such as neck nodal levels which are not first echelon nodes and are not adjacent to levels containing grossly involved nodes) will be prescribed 54 Gy/35 fractions

Treatment of the low neck: see details in Section 5.4.7. If the low neck is treated, the preferred technique is to treat with isocentric matching AP or AP-PA fields with larynx block, matched to the IMRT portals just above the arytenoids. The dose will be 2 Gy per fraction prescribed to 3 cm depth to a total dose of 50 Gy in 25 daily fractions. Whole-neck IMRT is allowed. Involved low neck nodes will receive total 70 Gy

in 35 fractions. This can be achieved by either boosting the low neck field with an additional 16 Gy in 8 fractions, by an AP or AP-PA fields, or by planning the whole neck using IMRT. In cases of gross involvement of the vallecula or low neck, whole-neck IMRT should be considered. Whole-neck IMRT may also be considered if level VI is considered to be at risk due to gross involvement of level IV nodes.

All plans must be normalized such that 95% of the volume of the PTV1 is covered with prescription dose of 70 Gy. Additionally: At 1 cc PTV1 volume on the DVH curve, the dose should not be > 110% of the prescribed dose. At a volume of 0.03 cc within the PTV1 volume on the DVH curve, the dose should not be < 95% of the prescribed dose. For any volume of tissue outside the PTVs that has a size of 1 cc, the dose should not be > 74 Gy.

**Lymph Node Regions**

a. Submental nodes *(level IA)*: In cases where the floor of mouth, oral tongue, or level IB are involved.

b. Submandibular nodes (*level IB)*: To be covered when the ipsilateral level II has nodal disease of at least 3 cm or the oral cavity is involved.

*c.* Upper deep jugular *(junctional, parapharyngeal)* nodes: all cases *(at the neck side ipsilateral to the primary tumor).*

d. Subdigastric *(jugulodigastric)* nodes, midjugular, lower neck, and supraclavicular nodes *(levels II through IV)*: all cases, bilaterally; unilateral neck treatment can be considered for well lateralized T1/2 primary tumors.

e. Posterior cervical nodes *(level V)*: all cases, at the neck side where there is evidence of jugular nodal metastases.

f. Medial retropharyngeal nodes: all cases involving the pharyngeal axis (i.e. not required for oral cavity and larynx cancers not involving pharyngeal structures) should be contoured from the level of C1 through the superior border of the hyoid body.

**Critical Normal Structures**

The normal tissue volume to be contoured will include the skin surface, brainstem, spinal cord, mandible, glottic larynx, supraglottis, esophagus, trachea, oral cavity, lips and parotid and submandibular salivary glands. The PRV (planning risk volume) spinal cord contours will be defined at least 0.5 cm larger in the radial dimension than the spinal cord *(i.e. the cord diameter on any given slice will be 1.0 cm larger than the cord itself*). The normal tissues will be contoured and considered as solid organs. The tissue within the skin surface and outside all other critical normal structures and PTVs is designated as unspecified tissue

### 5.4.4 Treatment Planning and Delivery

Megavoltage energy photon beam irradiation is required. Any treatment planning and delivery system that has been credentialed for head and neck IMRT for previous RTOG trials is acceptable.

### 5.4.5 Image Guidance for IGRT When Using Reduced Margins

Daily image guidance of IMRT may be achieved using any one or more of the following techniques:

- Orthogonal kilovoltage (KV) images, e.g. ExacTrac;

- Linear-accelerator mounted kV and MV helical conebeam CT images;
- Linear-accelerator mounted MV CT images (e.g., Tomotherapy);
- Other mechanism, after discussion with the Radiation Oncology Co-Chair, Jonathan J. Beitler, MD.

The institution's procedure for registering daily treatment imaging datasets with a reference dataset should comply with the following recommendations:

Region-of-Interest (ROI) or "clip box" for fusion should be set to encompass the high dose PTV and adjacent spinal cord; if the supraclavicular region is a part of the target volume the ROI should extend to the C6 level; If the fusion software allows the user to create an irregular ROI (e.g., ExacTrac), treatment room objects seen on in-room x-rays should be excluded from the registration; manual (e.g., based on bony anatomy) and automatic (e.g., based on mutual information) types of registration can be used; the result of the fusion must be visually checked for the alignment of the bony anatomy, such as vertebral bodies and applicable soft tissue structures (e.g., optic nerves and/or optic chiasm).

Following the registration, the translational and (if the appropriate technology is available) rotational corrections should be applied to the treatment couch. If all the variances are less than 2.5 mm (this typically corresponds to one half of the usual PRV margin), the treatment can proceed without correction (however, the physician/team may elect to perform adjustments even for a variance < 2.5 mm). If one or more corrections are 2.5-5 mm, adjustment is necessary prior to treatment; however, re-imaging is not mandatory. If one or more of the corrections are larger than 5 mm, the imaging must be repeated in addition to performing table/positioning adjustments. However, the use of numerous repeat IGRT studies should be avoided (see next section).

*Management of Radiation Dose to the Patient from IGRT*

Estimates of patient doses per imaging study for various imaging systems vary considerably. The doses are in the range of 1 mGy for Cyberknife's and BrainLab's ExacTrac planar kV- systems. The doses from helical MV CT scan on a tomotherapy unit were estimated to be in the range of 1 to 3 cGy for head and neck studies, similar to doses reported for kV cone beam CT on the Elekta Synergy machine. The doses for MV cone beam CT are in the range of 10 cGy for a pelvis study to 6 cGy for a head and neck study. Thus, the doses for 3D imaging systems are in the range from 1 to 6 cGy for head and neck imaging and can contribute from 0.5 to 3% to the daily dose of 2.0 Gy. These dose estimates apply to a single imaging procedure, and the 2 cGy dose is used as a typical fraction size for comparison purposes within the treated region. It is important to point out that the imaging dose typically covers parts of the patient's anatomy that are outside the high-dose region that is treated therapeutically, and that it is sometimes necessary to repeat the procedure a number of times during, before, or after a single fraction delivery. The imaging dose to nearby critical structures may become significant when repeated IGRT procedures are performed for patients with severe set up problems (e.g., requiring frequent corrections of more than 5 mm). It is recommended that patients demonstrating severe set up problems during the first week of treatment be moved to a treatment with larger margins.

### 5.4.6 Definition of Normal Tissues/Organs at Risk (OARs)

**NOTE**: **Only the parts of the normal tissues/organs at risk outside the PTVs will be considered for dose optimization purposes.**

*Spinal Cord*: The cord begins at the cranial-cervical junction (i.e. the top of the C1 vertebral body). Superior to this is brainstem and inferior to this is cord. The inferior border of the spinal cord is at approximately T3-4 (i.e., just below the lowest slice level that has PTV on it). The spinal cord shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) spinal cord shall be defined. The PRVcord = cord + 5 mm in each dimension. This is irrespective of whether or not IGRT is used.

*Brainstem*: The inferior most portion of the brainstem is at the cranial-cervical junction where it meets the spinal cord. For the purposes of this study, the superior most portion of the brainstem is approximately at the level of the top of the posterior clinoid. The brainstem shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) brainstem shall be defined. The PRVbrainstem = brainstem + 3 mm in each dimension.

*Lips and Oral Cavity*: These should be contoured as 2 separate structures as the goal is to keep the lip dose much lower than the oral cavity dose. The definition of lips is self-explanatory. The oral cavity will be defined as a composite structure consisting of the anterior ½ to $^{2}/_{3}$ of the oral tongue/floor of mouth, buccal mucosa, and palate.

*Parotid Glands*: Parotid glands will be defined based on the treatment planning CT scan.

*OARpharynx*: This will be defined as the "uninvolved" posterior pharyngeal wall plus adjacent constrictor muscles. This extends from the superior constrictor region (the inferior pterygoid plates level) to the cricopharyngeal inlet (posterior cricoid cartilage level).

*Cervical Esophagus*: This will be defined as a tubular structure that starts at the bottom of OARpharynx and extends to the thoracic inlet.

*Glottic/Supraglottic Larynx (GSL)*: This will be defined as a "triangular prism shaped" volume that begins just inferior to the hyoid bone and extends to the cricoid cartilage inferiorly and extends from the anterior commissure to include the arytenoids. This includes the infrahyoid but not suprahyoid epiglottis.

*Mandible*: This includes the entire boney structure of the mandible from TMJ through the symphysis.

*Unspecified Tissue Outside the Targets*: This will be defined as tissue located between the skull base and thoracic inlet that is not included in either the target volumes or the normal tissues described above.

In cases of weight loss > 10% or significant shrinkage of lymphadenopathy during therapy, it is recommended that the immobilization mask will be adjusted or re-made in order t o preserve

adequate immobilization, and that a repeated simulation CT be performed to assess the dose distributions in the current anatomy. Whether or not a new IMRT plan will be generated is at the discretion of the treating physician. If a new plan is made, the targets should be the same as those used for the initial plan. The new CT dataset should be used for IGRT image registration when the patient's shape changes significantly.

### 5.4.7 Management of the Low Neck/Supraclavicular Region (Match versus No Match)

It is recognized that comprehensive head and neck irradiation incorporating IMRT can be done in several ways, any of which is permitted for this study. Patient-specific QA measurements are required for all IMRT treatments. When a field "match" technique is used for treating the lower neck, patient-specific measurements should include a verification of the dose coverage in the gap region for each patient.

1. Match: The upper cervical lymphatics and primary tumor bed are treated with IMRT. The lower cervical lymphatics and supraclavicular region are treated with a single AP (or occasionally APPA for larger patients with posterior neck at high risk) non-IMRT technique. The latter non-IMRT field(s) is matched to the upper neck IMRT fields. This technique requires comprehensive mid-line spinal cord blocking in the lower neck fields. This technique also allows for a simultaneous blocking of portions of the larynx, hypopharynx, and cervical esophagus in the lower neck fields. Matching 2 IMRT plans is allowed.
2. No Match: The entire clinical target volume (CTV) [upper and lower neck and primary tumor bed] is irradiated with IMRT. There is no match line between upper and lower portions of the regions at risk. In this technique, limiting radiotherapy dose to organs at risk (OARs), e.g., the cervical esophagus, is entirely achieved by inverse treatment planning via IMRT algorithms.

### 5.4.8 Dose Prescription

Doses to PTVs

See Sections above for definitions of CTVs and PTVs and their prescribed doses. The goal is for 95% of the PTV70 to receive ≥ 2 Gy with a minimum dose (cold spot) of no less than 66.5 Gy. It is recognized that portions of the PTV70 close to the skin may receive significantly less than 66.5 Gy. This is acceptable as long as cold spots within PTV1 do not exist at a depth deeper than 8 mm beneath the skin.

For planning prioritization and priorities in dose coverage, in the final plan, PTV1 will be the highest priority target structure. PTV2 and PTV3, if applicable, will be ranked in the IMRT planning as lower priority than PTV1 although usually at a higher priority than normal structures other than spinal cord and brain stem.

Doses to Normal Structures

*Spinal Cord:* The PRVcord (as defined in Section 5.3.6.) should not exceed ≤ 50 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). In treatment planning, the spinal cord PRV should be given the highest priority.

*Brainstem*: The PRVbrainstem (as defined in Section 5.3.6.) should not exceed 52 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). In treatment planning, the PRVbrainstem should be given less priority than the PRVcord but more priority than the other critical structures listed below.

*Lips:* Reduce the dose as much as possible. The mean dose should be < 20 Gy. This may be exceeded in oral cavity cancers.

*Oral Cavity:* Reduce the dose as much as possible. The mean dose should be < 30 Gy for the non-involved oral cavity. Efforts should also be made to avoid hot spots (> 60 Gy) within the non-involved oral cavity.

*Parotid Glands*: In most cases, it will be easier to spare one parotid than the other. The treatment planning goal will be for this individual parotid gland to receive a mean dose of < 26 Gy. Taking into account new data suggesting monotonous improvement in saliva as dose is reduced, without a threshold (Dijkema 2010), the objective will be to reduce the mean doses to both parotid glands as much as possible.

*Contralateral submandibular gland*: If contralateral level I is not a target, aim to reduce mean contralateral submandibular gland to < 39 Gy.

*OARpharynx*: Reduce the dose as much as possible. Some recommended (but not mandatory) treatment goals include: 1) No more than 33% of the OARpharynx exceeds 50 Gy; 2) Mean dose < 45 Gy; 3) No more than 15% of the OARpharynx exceeds 60 Gy.

*Cervical Esophagus*: Reduce the dose as much as possible. Some recommended (but not required) treatment goals include: Mean dose < 30 Gy.

*Glottic and Supraglottic larynx (GSL)*: Reduce the dose as much as possible. The glottic larynx me a n dose is recommended to be ≤ 20 Gy. If whole-neck IMRT is used, under- dosage of PTV2/PTV3 adjacent to the glottic larynx will be limited to < 10% receiving < 95% prescribed dose (this under-dosage is similar to that caused by the laryngeal block inserted in the split-field IMRT; Webster 2009).

*Mandible:* Reduce the dose as much as possible. Hot spots within the mandible should be avoided. It is recommended that maximum dose within the mandible be < 66 Gy, except in areas overlapping PTV.

*Unspecified Tissue Outside the Targets*: No more than 1cc of unspecified tissue outside the targets can receive 74 Gy or more

### 5.4.9 Planning Priorities and Goals

1. Spinal Cord
2. Brainstem
3. PTV1
4. PTV2 (if applicable)
5. PTV3 (if applicable)
6. a. OARpharynx
   b. Parotid gland contralateral to primary tumor site
7. a. GSL
   b. Esophagus
8. a. Lips
   b. Oral Cavity
9. a. Parotid gland ipsilateral to primary tumor site
   b. Mandible
10. Unspecified tissue outside the targets

### 5.4.10 Critical Structures

**Note: All required structures must be labeled as listed in the table below for digital RT data submission. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed.**

Table 8 outlines the naming of the various normal and critical structures for submission to TRIAD.

**Table 8. Standard Nomenclature for Normal and Critical Structures**

| Standard Name | Description | Reference Dose (Gy) |
|---|---|---|
| | | |
| GTV | Primary tumor and involved | 70 |
| CTV70 | Primary tumor and involved | 70 |
| PTV70 | CTV to PTV expansion should be 5 mm minimal margin without | 70 |
| CTV_60 | First Echelon nodal regions | 60 |

| | | |
|---|---|---|
| PTV60 | CTV to PTV expansion should be 5<br>mm minimal margin without | 60 |
| CTV50 | Lower risk nodal regions | 50 |
| PTV50 | CTV to PTV expansion should be 5 mm minimal margin without IGRT+ | 50 |
| CTV54 | Lower risk nodal regions | 54 |
| PTV54 | CTV to PTV expansion should be 5 mm minimal margin without IGRT; 3 mm | 54 |
| SpinalCord | Spinal Cord | ≤ 48 |
| SpinalCord_05 | Planning risk Volume of 5 mm | ≤ 50 |
| BrainStem | Brain Stem | ≤ 50 |
| BrainStem_03 | Planning Risk Volume of 3 mm | ≤ 52 |
| Parotid | Mean doses to one Parotid | ≤ 26 |
| OralCavity (excluding PTV's) | Oral Cavity | Mean dose ≤ 32 |
| Mandible (excluding PTV's) | Mandible | D0.03cc < 66 |
| OARPharynx | Uninvolved posterior pharyngeal wall<br>plus adjacent constrictor muscles; | Mean dose ≤ 40 |
| Esophagus_Up | Cervical Esophagus | Mean dose ≤ 30 |
| Larynx | Glottic/Supraglottic Larynx | Mean dose ≤ 35 |
| NonPTV_7000 | Maximum dose (hot spot > 1cc outside the PTVs) | D1cc < 63 |

### 5.4.11 Image-Guided Radiotherapy

Daily image guidance of IMRT may be achieved using any one or more of the following techniques:

- Orthogonal kilovoltage (KV) images.
- Linear-accelerator mounted kV and MV cone-beam CT images (CBCT).

### 5.4.12 Radiation Therapy Treatment Interruptions

Treatment interruptions are strongly discouraged. Treatment breaks must be clearly indicated in the treatment record when they occur. Patients who have treatment interruptions for > 3 weeks will be taken off study. The interruption of radiation therapy for grade 4 mucositis / dermatitis / dysphagia is at the discretion of the treating radiation oncologist. Treatment breaks, if necessary, ideally should not exceed five treatment days at a time and ten treatment days total. Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and not for social or logistical reasons. Cisplatin and pembrolizumab will not be administered during radiotherapy treatment breaks.

### 5.4.13 Radiation Therapy Adverse Events

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4 will be utilized for grading all adverse events. All appropriate treatment areas should have access to a copy of the CTCAE, v. 4. A copy of the CTCAE, v. 4 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

Grade 3 therapy-induced mucositis and/or dysphagia are expected to develop in about one third to one half of patients. Nutritional evaluation prior to the initiation of therapy for a prophylactic gastrostomy (PEG) tube placement is highly recommended. Placement of a feeding tube should be recorded on the appropriate case report form, as should use of a feeding tube during and after treatment (e.g., greater than or less than 50% of nutrition by tube). Other common radiation adverse events include: fatigue, weight loss, regional alopecia, loss of teeth or cavities, xerostomia, hoarseness, transient ear discomfort, dysgeusia, increased sensitivity of the skin to hot and cold temperature as well as the sun and skin erythema and desquamation within the treatment fields.

Less common long-term treatment adverse events include: hypothyroidism, loss of hearing, chronic swallowing dysfunction requiring permanent feeding tube, brachial plexopathy, and cervical fibrosis. Much less common radiation adverse events include: mandibular osteoradionecrosis (< 5% incidence with attention to dental recommendations), and cervical myelopathy (< 1% with restriction of spinal cord dose to ≤ 45 Gy).

Rare but serious side effects that may develop including fibrotic tissue formation, soft tissue ulceration and/or irritation or damage to the skin within the neck that may result in bleeding. Blindness and the development of secondary (new) cancers and tumors is very rare but also possible.

## 5.5 Duration of Treatment and Follow-up

Complete treatment includes the course of definitive radiotherapy with concurrent chemotherapy and a total of 8 doses of pembrolizumab. In the absence of treatment delays due to adverse event(s), treatment may continue until disease progression or until one of the following criteria applies:

- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),

- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment inthe judgment of the investigator.

Patients will be followed for progression and survival every 3 months for two years, then every 6 months for one year, then annually for two years after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

## 5.6 Patient Discontinuation

Subjects who meet the following criteria should be discontinued from study treatment:

- Inability of subject to comply with study requirements.
- The patient elects to withdraw from the study for any reason.
- Determination by the investigator that it is no longer safe for the subject to continue therapy.
- Disease progression - patients who undergo surgical consolidation and are found to have residual disease are not considered to have disease progression.

## 5.7 Dose Limiting Toxicity (DLT)

Dose Limiting Toxicity will be continuously monitored in both treatment arms, and is explicitly intended for the purposes of safety monitoring of the concurrent combination of pembrolizumab and cisplatin-IMRT (Arm 2). As defined, excess DLT is not expected during standard of care cisplatin-IMRT. Excess DLT in either arm, however, would trigger the early stopping rule. Please see Section 10.3 for details of the early stopping rule.

### 5.7.1 DLT

DLT is defined as the occurrence of a severe adverse event (AE) listed below that is *at least possibly* related to pembrolizumab and occurs within 24 weeks of the initiation of pembrolizumab on either treatment arm. AEs will be graded according to NCI CTCAE version 4.0.

**DLT Definition:**

Since autoimmune/inflammatory events may occur at any time during the course of treatment, and may occur with evidence of clinical benefit, the following criteria will be used to define DLT:

- Any ≥ Grade 4 non-hematologic toxicity **except**:
    - Grade 4 in-field radiation dermatitis for which IMRT is held ≤ 1 week (5 fractions).
    - Grade 4 mucositis for which IMRT is held ≤ 1 week (5 fractions).
    - Asymptomatic Grade 4 hypomagnesemia or hypokalemia, which corrects to Grade ≤ 2 with replacement therapy.
- An alanine or aspartate amino transaminase elevation of greater than three times the upper limit of normal with concurrent elevation of bilirubin two times the upper limit of normal attributable to pembrolizumab should be considered a DLT. Patients meeting this criterion should be permanently discontinued from pembrolizumab.
- Autoimmune toxicity of any grade requiring systemic corticosteroids or other anti-inflammatory that cannot be tapered off in less than 12 weeks.
- Delay in completion of radiation therapy >10 fractions, or inability to complete prescribed IMRT course, due to immune toxicity at least possibly attributed to pembrolizumab.
- Grade ≥ 3 neutropenia with fever (oral temperature > 39°C).
- Grade ≥ 3 thrombocytopenia with bleeding.

Patients who experience a DLT will receive no additional doses of pembrolizumab and will be withdrawn from the protocol. Patients may complete cisplatin and radiation per standard of care.

## 6. RESPONSE ASSESSMENT

Patients will undergo clinical head and neck exam and post-treatment CT scan with IV contrast 12-14 +/- 2 weeks following completion of IMRT. Note, an integrated PET/CT with contrasted diagnostic CT scan is recommended if feasible at the participating site; however, only a diagnostic CT scan is required. Rare patients may require an MRI for tumor measurements, due to allergy to iodinated contrast despite premedication. In these patients, MRI of the neck should be performed at baseline and at first response assessment.

Responses will be coded for:

- Clinical examination response, primary and nodes.
- CT response, primary and nodes (see modified RECIST criteria version 1.1, Section 6.1).

- If applicable: Integrated PET/CT response, primary and nodes (see Integrated PET/CT response criteria, Section 6.2.4). Solid Tumor Response Criteria (modified RECIST Criteria version 1.1)

### 6.1.1 Malignant Disease Evaluation

To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. Measurable disease is defined by the presence of at least one measurable lesion.

All measurements should be recorded in metric notation by use of a ruler or calipers. The same method of assessment and the same technique should be used to characterize each identified lesion at baseline and during follow-up. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks before registration.

The term unevaluable in reference to measurability will not be used because it does not provide additional meaning or accuracy. At baseline, the primary tumor and pathologic neck lymph nodes will be characterized as either measurable or non-measurable.

#### 6.1.1.1 Measurable Disease

##### 6.1.1.1.1 Primary Tumor

Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm (2.0 cm) with conventional techniques or as ≥ 10 mm (1.0 cm) with spiral CT scan.

##### 6.1.1.1.2 Neck Lymph Nodes

Neck lymph nodes are considered pathologic and measurable if short axis ≥ 15 mm.

Neck lymph nodes are considered pathologic but non-measurable if short axis ≥ 10 mm but < 15 mm. Neck lymph nodes are considered non-pathologic and non-measurable if short axis < 10 mm.

#### 6.1.1.2 Non-measurable disease

All other lesions, including small lesions [longest diameter < 20 mm (2.0 cm) with conventional techniques or < 10 mm (1.0 cm) with spiral CT scan] are truly non-measurable lesions.

Lesions considered to be truly non-measurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion,

inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

### 6.1.2 Definitions of a Response

#### 6.1.2.1 Target Lesions

All measurable lesions, including the primary tumor, and up to a maximum of five neck lymph nodes, should be measured at baseline.

The sum of the longest diameter of the primary tumor, and the short axis diameter of target pathologic lymph nodes, will be calculated at baseline and reported as the *baseline sum diameter*.

##### 6.1.2.1.1 Complete Response (CR)

The disappearance of the primary tumor and the resolution of pathologic neck adenopathy. For the definition of radiographic complete response in the neck, the resolution of neck lymph nodes to < 10 mm in short axis diameter with non-pathologic appearance is sufficient.

##### 6.1.2.1.2 Partial Response (PR)

At least a 30% decrease in the sum of target lesion diameters (longest diameter of the primary tumor; short axis diameter of the target lymph nodes), taking as reference the *baseline sum diameter*.

##### 6.1.2.1.3 Progressive Disease (PD)

At least a 20% increase in the sum of target lesion diameters (longest diameter of the primary tumor; short axis diameter of the target lymph nodes), taking as reference the *smallest sum diameter* recorded since the baseline sum diameter measurements, or the appearance of one or more new lesion(s).

##### 6.1.2.1.4 Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

#### 6.1.2.2 Non-target Lesions

All other lesions or sites of disease. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

##### 6.1.2.2.1 Complete Response (CR)

The disappearance of all nontarget lesions and normalization of tumor marker levels, if applicable.

#### 6.1.2.2.2 Partial Response (PR)/Stable Disease (SD)

The persistence of one or more nontarget lesion(s).

#### 6.1.2.2.3 Progressive Disease (PD)

The appearance of one or more new lesion(s) and / or unequivocal progression of existing non target lesions.

### 6.1.2.3 Symptomatic Deterioration

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having *symptomatic deterioration*.

### 6.1.3 Evaluation of Patient's Best Overall Response

The best overall response is the best response recorded from registration until disease progression/recurrence, taking as reference for progressive disease the smallest measurements recorded since registration. Table 9 below provides overall responses for all possible combinations of tumor responses in target and nontarget lesions, with or without new lesions.

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of eight weeks.

**Table 9. Overall Response for all Possible Combinations of Tumor Response**

| Target Lesions | Nontarget Lesions | New Lesions | Overall Response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Incomplete response/SD | No | PR |
| PR | Non-PD | No | PR |
| SD | Non-PD | No | SD |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease

**NOTE: BOTH CLINICAL (by ENT examination) AND RADIOGRAPHIC RESPONSE (by CT or MRI scan) will be recorded. Response in the primary and the neck will be reported separately.**

#### 6.1.3.1 First Documentation of Response

The time between initiation of therapy and first documentation of PR or CR.

#### 6.1.3.2 Confirmation of Response

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

#### 6.1.3.3 Duration of Response

Duration of overall response - the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded since treatment started.

#### 6.1.3.4 Duration of Overall Complete Response

The period measured from the time measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

#### 6.1.3.5 Duration of Stable Disease

A measurement from registration until the criteria for disease progression is met, taking as reference the smallest measurements recorded since registration. To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of six weeks.

#### 6.1.3.6 Survival

Survival will be measured from the date of entry on study.

#### 6.1.3.7 Time to Progression and Progression-free survival

This interval will be measured from the date of entry on the study to the appearance of new metastatic lesions or objective tumor progression. Progression-free survival (PFS) will be calculated from treatment initiation to disease progression or death from any cause or last follow up.

## 6.2 Methods of Measurement

Imaging based evaluation is preferred to evaluation by clinical examination. The same imaging modality must be used throughout the study to measure disease.

### 6.2.1 CT and MRI

CT and magnetic resonance imaging (MRI) are the best currently available and most reproducible methods for measuring target lesions. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed by use of a 5 mm contiguous reconstruction algorithm. This specification applies to tumors of the chest, abdomen, and pelvis, while head and neck tumors, and those of the extremities require specific procedures.

### 6.2.2 Clinical Examination

Evaluation of measurable disease in the primary site as well as nodal sites by ENT examination should be recorded at baseline. Determination of complete response will occur through radiologic imaging as well as the post-protocol endoscopic examination.

### 6.2.3 Cytology and Histology

Cytologic and histologic techniques can be used to differentiate between complete and partial response in rare cases (e.g., after treatment to differentiate residual benign lesions and residual malignant lesions in germ cell tumors). Cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met response or stable disease criteria.

Should primary site biopsy, primary site salvage, and/or neck dissection be conducted, the pathologic response will be recorded.

### 6.2.4 FDG-PET Scan

The ideal post-chemoradiotherapy response assessment method would accomplish two goals: 1) accurately detect viable residual disease amenable to surgical consolidation and 2) be prognostic for longer term clinical outcomes including PFS. Head and neck clinical examination alone has an accuracy of less than 50% for residual neck nodal disease,[63] while post-radiation diagnostic CT has higher sensitivity than clinical exam but unsatisfactory specificity.[64,65] An increasing body of literature suggests that post-chemoradiotherapy positron emission tomography (PET), performed 8-12 weeks following completion of radiotherapy has improved accuracy relative to CT for classification of complete response in PULA HNSCC. The negative predictive value (NPV) for determination of residual neck disease, in particular, ranges from 92-100%.[66-69] The University of Pittsburgh institutional experience indicates that serial PET/CT scans permit safe deferral of planned neck dissection following chemoradiotherapy. Moreover, a PET scan added to a diagnostic contrasted CT is superior to clinical examination or diagnostic CT alone

(utilizing RECIST criteria 1.0) with regard to correlation with PFS.[70] However, RECIST 1.0 criteria were developed primarily for response assessment in the metastatic solid tumor setting, where patients are treated with palliative systemic therapy. RECIST 1.0 criteria inadequately address the post-chemoradiotherapy setting. Specifically, a CR in accordance with RECIST 1.0 requires disappearance of all target lesions, including pathologic lymph nodes. However, non-pathologic, subcentimeter lymphadenopathy can persist after chemoradiotherapy. RECIST 1.1 now incorporates new guidelines for the measurement of nodal disease, and for determination of CR, a short axis of < 1 cm is no longer considered residual disease. The accuracy of the RECIST 1.1 criteria for assessment of residual disease or as a predictor of PFS following chemoradiotherapy for PULA HNSCC is not reported.

To date, the majority of PET/CT literature conducted has been retrospective. The sole prospective study of PET/CT versus CT for first response assessment following chemoradiotherapy was performed at MDACC.[66] This study found that PET/CT was not superior to diagnostic CT alone for the accuracy of response assessment in unselected PULA HNSCC patients. However, in high risk patients defined as HPV-negative, non- oropharynx, and/or tobacco-exposed, PET/CT outperformed CT. The study has been criticized for lack of integration of a diagnostic contrasted CT into the PET/CT acquisition algorithm, although PET/CT results were interpreted with knowledge of a separate contrasted diagnostic CT; such integration enhances per-lesion sensitivity and specificity in head and neck cancer staging[71] and is of theoretical utility in the post-treatment patient. The CT criteria used in the MDACC study to classify nodal disease were clinical and related to RECIST. However, long axis nodal measurements were utilized with the following categorization:

- Pathologic (residual disease) nodes: > 15 mm in longest diameter and/or necrotic appearance.
- Indeterminate nodes: 10-15 mm in longest diameter and non-specific CT findings.
- Non-pathologic nodes: < 10 mm in longest diameter and non-necrotic (CR).

At the University of Pittsburgh, the standard of care following definitive chemoradiotherapy for PULA HNSCC has been integrated PET/CT. Following PET/CT patients are placed into four clinical categories: Negative PET/CT (Complete Response); Probably Negative PET/CT (Low clinical concern; follow up indicated); Probably Positive PET/CT (Clinical concern; tissue sampling indicated); Positive PET/CT (Definite residual disease). This categorization has been found to correlate with clinical outcomes, specifically PFS.[72]

Definition of CR following chemoradiotherapy therefore has two relevant, literature-based definitions which may be of clinical utility: 1) Quantitative anatomic criteria (RECIST 1.1); 2) Integrated PET/CT criteria.

**Complete Response: Modified RECIST 1.1 (see section 6.1)**

- Disappearance of primary tumor. Irregular contour of the tumor bed is consistent with -radiation change.
- Decrease in measurable pathologic neck lymph nodes to short axis measurement < 10 mm and non-necrotic appearance with normalization of nodal configuration. Increased enhancement may be attributable to radiation change.
- No new pathologic lesions.

# 7. DRUG INFORMATION

## 7.1 Pembrolizumab

### 7.1.1 Study Drug Materials

Pembrolizumab drug substance is produced at two locations to yield: 1) a partially formulated aqueous solution stored under refridgerated conditions (2-8˚C) at a concentration of 40-50 mg/mL in 10 mM histidine buffer, pH 5.2-6.8, and 2) a fully formulated aqueous solution stored frozen (-40˚C) at a concentration of 22.5-27.5 mg/mL in 10 mM histidine buffer, pH 5.2-5.8 containing 7% sucrose and 0.02% polysorbate 80. The drug products are sterile filtered into Type I glass vials intended for single use.

Two drug product dosage forms are available for pembrolizumab: 1) a white to off-white lyophilized powder, 50 mg/vial, and 2) a liquid, 100 mg/vial.

- Pembrolizumab Powder for Solution for Infusion, 50 mg/vial (manufactured using the partially formulated drug substance), is reconstituted with sterile water for injection prior to use. It is formuated with L-histidine as buffering agent, polysorbate 80 (surfactant), sucrose as stabilizer/tonicity modifier, and hydrochloric acid (HCl) and/or sodium hydroxide (NaOH) for pH adjustment (if necessary).
- Pembrolizumab Solution for Infusion, 100 mg/vial is a liquid drug product (manufactured using the fully formulated drug substance), and has the identical formulation as that of the reconstituted lyophilized vial.

The product after reconstitution with sterile water and the liquid drug product are a clear to opalescent solution which may contain proteinaceous and extraneous particulates.

Both the pembrolizumab reconstituted product and the liquid product are intended for IV administration and both can be further diluted with normal saline in IV containers made of polyvinyl chloride (PVC) or non-PVC material.

### 7.1.2 Pembrolizumab Study Drug Storage

Both pembrolizumab drug product dosage forms are to be stored under refrigerated conditions (2° C– 8°C) and in a secure location.

Note: No other use of pembrolizumab study drug intended for use in this trial is authorized by the sponsor. The investigator (or designee) will be responsible for the appropriate handling and disposition of residual study drug in partially used vials.

Vial Labels: Pembrolizumab vial labels will bear the appropriate label text for investigational agents, as required by governing regulatory agencies.

Complete study drug information (including packaging, labeling, storage and disposition) is provided in the Pembroliuzumab Investigator's Brochure (IB).

## 7.2 Cisplatin

Refer to the package insert for additional information.

Formulation: Each vial contains 10 mg of DDP, 19 mg of sodium chloride, 100 mg of mannitol, and hydrochloric acid for pH adjustment. One vial is reconstituted with 10 ml of sterile water. The pH range will be 3.5 to 4.5. Cisplatin injection also is available from the manufacturer in aqueous solution, each ml containing 1 mg cisplatin and 9 mg NaCl and HCL or NaOH to adjust pH.

Mechanism of Action: The dominant mode of action of cisplatin appears to be inhibition of the incorporation of DNA precursors, although protein and RNA synthesis are also inhibited. Although this drug seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents.

Administration: Cisplatin will be given as a bolus, infused over 1-2 hours along with appropriate hydration and anti-emetics.

Storage and Stability: Reconstituted solution of cisplatin is stable for 20 hours when stored at 27°C and should be protected from light if not used within 6 hours. The vials and injection should not be refrigerated. Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes.

Adverse Events: Human toxicity includes nausea, vomiting, renal toxicity (with an elevation of BUN and creatinine and impairment of endogenous creatinine clearance, as well as renal tubular damage, which appears to be transient), ototoxicity (with hearing loss that initially is in the high-frequency range, as well as tinnitus), and hyperuricemia. Much more severe and prolonged toxicity has been observed in patients with

abnormal or obstructed urinary excretory tracts. Myelosuppression, often with delayed erythrosuppression, is expected.

Supply: Cisplatin is commercially available. The use of drug(s) or combination of drugs in this protocol meets the criteria described under Title 21 CFR 312.2(b) for IND exemption.

## 8. CLINICAL AND LABORATORY EVALUATIONS

Schedule of Assessments. See Appendix C for Study Calendar.

### 8.1 Pre-Registration Evaluations

**NOTE: This section lists baseline evaluations that are required for registration. Evaluations should be performed within 4 weeks of registration unless otherwise indicated.**

### 8.1.1 Required Pre-Registration Evaluations

- History and physical examination, including vital signs, weight, height and ECOG performance status determination.
- Complete blood count, including platelets and differential.
- Blood chemistry studies (may be obtained from whole blood or serum/plasma samples), including BUN, creatinine, electrolytes ($K^+$, $Na^+$, $Cl^-$, $CO_2$), glucose, calcium, $Mg^{++}$ and liver function tests (total protein, albumin, total bilirubin, AST (SGOT), ALT (SGPT), and alkaline phosphatase), uric acid, and lactate dehydrogenase.
- Coagulation studies, including prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT).
- Thyroid function tests, including thyroid stimulating hormone (TSH), free thyroxine, (FT4), anti-thyroglobulin antibody, thyroid peroxidase antibody, thyroid stimulating immunoglobulin, and ANA. Establishing baseline thyroid function and pre-existing thyroid auto- immunity is required, as an appropriate clinical standard prior to chemoradiotherapy for HNSCC as well as anti-PD1 therapy for HNSCC. However, normal thyroid function and absence of subclinical thyroid auto-immunity (example detectable anti-thyroglobulin antibody or detectable thyroid peroxidase antibody) are not eligibility criteria. If subclinical hypothyroidism is detected, treatment should be initiated according to standard practice. If subclinical thyroid auto-immunity is detected, the patient is still eligible.
- For women of child bearing potential: Urine or blood pregnancy test within 2 weeks of registration to rule out pregnancy. (Note, pregnancy test will be repeated within 3 days of initiating protocol treatment.)
- Baseline tumor measurements within 4-6 weeks prior to registration. Contrasted diagnostic CT scan for staging and baseline tumor measurements. In the rare case that a patient is not a candidate for contrasted diagnostic CT scan (e.g. history of allergic reaction to iodinated contrast despite premedication), MRI of the neck may be conducted for baseline tumor measurements. **Note**: when feasible, a baseline integrated PET/CT with diagnostic contrasted CT scan is preferred. Any scans or x-rays used to document measurable disease should be done as close to study entry as possible and within 4 weeks prior to registration.

- Evaluation by an otolaryngologist with endoscopy as indicated, within 8 weeks prior to registration. Endoscopy for oropharyngeal carcinoma may be performed as clinically indicated. Endoscopy is required for hypopharyngeal and laryngeal carcinoma.
- For oropharyngeal or unknown primary cases: HPV status must be known or established and recorded at baseline.
- Tobacco history assessment form (See Appendix A).

### 8.1.2 Recommended Pre-Treatment Evaluations

*Note: This section lists baseline evaluations recommended but not required before the initiation of protocol treatment. These evaluations do not affect eligibility.*

- An audiogram within 12 weeks prior to start of protocol treatment and 8 to 12 weeks after IMRT is complete
- Dental evaluation and if applicable, prophylaxis, within 12 weeks prior to the start of protocol treatment. Prior to treatment, patients should be evaluated by a dental professional and receive clearance to initiate radiotherapy. A delay of at least 10 calendar days from major oral surgery, including dental extractions, is recommended prior to first radiotherapy treatment.
- Patients should be provided with dental education including the risk for radiation-induced dental decay, methods for maintaining good oral hygiene, and use of prescription fluoride treatment. Appropriate oral hygiene includes the following: brushing teeth after each meal, flossing daily, the frequent use of oral rinses with Salt and/or Baking Soda (every two to four hours), and the daily use of prescription fluoride therapy.
- Nutritional Evaluation. It is strongly encouraged that all patients undergo an initial dietary assessment by a trained dietician, prior to start of protocol treatment. Patients with weight loss and inadequate oral intake should be strongly considered for a feeding tube prior to initiation of therapy. For patients with adequate oral intake, the prophylactic placement of a feeding tube is at the discretion of the treating physician. Patients should be followed by dieticians routinely throughout the course of treatment. Dietary recommendations should include: recommended total caloric intake, recommended intake of protein, daily requirement for free water, and the appropriate use of

supplements. Should it become evident at any time during therapy that oral intake is inadequate, a feeding tube should be placed. Close monitoring by dieticians is important for patients with feeding tubes, particularly immediately after tube placement as patients often experience problems with enteral feeding or formulations. All patients who have a feeding tube placed should be referred to Speech and Language Pathology (SLP) for swallowing exercises to minimize disuse atrophy. In addition, post-treatment, it is critical to work with the SLP and dietician to identify when it is safe and appropriate for patients to return to oral intake. Patients should be encouraged to wean themselves off their feeding tubes as soon as possible in order to maximize swallowing outcomes.

- Speech and Language Pathology (SLP). It is strongly encouraged that all patients undergo swallowing assessment and therapy prior to the start of protocol treatment. Swallowing assessment and therapy should be considered a critical component of care for all head and neck cancer patients undergoing concurrent therapy. Assessments should be done by a trained Speech-Language Pathologist. SLP should be consulted during treatment planning and should provide routine follow-up throughout the trajectory of the patient's treatment and recovery. The treating physician should communicate with SLP in order to coordinate care in those patients found to have significant swallowing abnormalities. Critical component of the swallowing evaluation should include: 1) identification of any swallowing abnormalities, 2) recommendations for further testing, 3) formation of a treatment plan, 4) dietary recommendations and 5) clear identifications of patients at risk for aspiration. Patients should be referred immediately for evaluation if any of the following "trigger symptoms" are identified: coughing or clear the throat before, during or after eating, inability to control food, liquids or saliva in the oral cavity, complaint of difficulty swallowing or food "sticking" in the throat, nasal regurgitation of food, or pocketing of food in the cheek.

## 8.2 Evaluations during treatment

### 8.2.1 Arm 1 (Cisplatin-IMRT followed by sequential pembrolizumab)

**ARM 1, WEEKS 1-7 (During**

**concurrent cisplatin-IMRT)**

**Weekly:**

*Note: The following assessments will be performed weekly and may be performed on the day of or the day prior to cisplatin administration.*

- History and physical examination.
- Vital signs, including weight.
- Toxicity assessment with attribution.
- Update of concomitant medications.

- Complete blood count, including platelets and differential.
- Blood chemistries (may be obtained from whole blood or serum/plasma sample), including creatinine, electrolytes (K+, Na+, CI-, CO2), calcium, Mg++ and liver function tests [bilirubin, AST (SGOT), ALT (SGPT), and alkaline phosphatase, total protein, albumin].

**Every 3 weeks (Week 3 and Week 6):**

*Note: The following assessments will be performed every 3 weeks during concurrent cisplatin-IMRT and may be performed on the day of or the day prior to cisplatin administration. It is recommended that research blood should be coupled to the standard of care blood draw, to minimize needle sticks to the patient.*

- Thyroid function tests (TSH, FT4).

**Once (Week 6):**

- Anti-thyroglobulin antibody, thyroid peroxidase antibody, thyroid stimulating immunoglobulin, and ANA.

**ARM 1, WEEKS 8-31 (During sequential**

**pembrolizumab treatment): Every 3**

**weeks (Week 9, 12, 15, 18, 21, 24, 25,**

**30):**

*Note: The following assessments will be performed every 3 weeks, and may be performed on the day of or the day prior to pembrolizumab administration.*

- History and physical examination.
- Vital signs, including weight.
- Toxicity assessment with attribution, including irAE assessment.
- Update of concomitant medications.
- Complete blood count, including platelets and differential.
- Blood chemistries (may be obtained from whole blood or serum/plasma sample), including creatinine, electrolytes (K+, Na+, CI-, CO2), calcium, Mg++ and liver function tests [bilirubin, AST (SGOT), ALT (SGPT), and alkaline phosphatase, total protein, albumin] .
- Thyroid function tests (TSH, FT4).

**Twice (Week 18, Week 30; these will be performed at the 4th and 8th doses of pembrolizumab, respectively):**

- Anti-thyroglobulin antibody, thyroid peroxidase antibody, thyroid stimulating immunoglobulin, and ANA.

### 8.2.2 Arm 2 (Concurrent pembrolizumab, cisplatin and IMRT)

**ARM 2, WEEKS -1 to +7 (During concurrent**

**pembrolizumab, cisplatin-IMRT) Weekly:**

*Note: The following assessments will be performed weekly starting Week -1, and may be performed on the day of or the day prior to pembrolizumab and/or cisplatin administration.*

- History and physical examination.
- Vital signs, including weight.
- Toxicity assessment with attribution, including irAE assessment.
- Update of concomitant medications.
- Complete blood count, including platelets and differential.
- Blood chemistries (may be obtained from whole blood or serum/plasma sample), including creatinine, electrolytes (K+, Na+, CI-, CO2), calcium, Mg++ and liver function tests [bilirubin, AST (SGOT), ALT (SGPT), and alkaline phosphatase, total protein, albumin].

**Every 3 weeks (Week 3 and Week 6):**

*Note: The following assessments will be performed every 3 weeks during concurrent pembrolizumab, cisplatin-IMRT, and may be performed on the day of or the day prior to cisplatin/pembrolizumab administration. It is recommended that research blood should be coupled to the standard of care blood draw, to minimize needle sticks to the patient.*

- Thyroid function tests (TSH, FT4).

**Once (Week 6):**

- Anti-thyroglobulin antibody, thyroid peroxidase antibody, thyroid stimulating immunoglobulin, and ANA.

**ARM 2, WEEKS 8-25 (During sequential**

**pembrolizumab treatment): Every 3**

**weeks (Week 9, 12, 15, 18, 21):**

*Note: The following assessments will be performed every 3 weeks, and may be performed on the day of or the day prior to pembrolizumab administration.*

- History and physical examination.
- Vital signs, including weight.
- Toxicity assessment with attribution, including irAE assessment.
- Update of concomitant medications.

- Complete blood count, including platelets and differential.
- Blood chemistries (may be obtained from whole blood or serum/plasma sample), including creatinine, electrolytes (K+, Na+, CI-, CO2), calcium, Mg++ and liver function tests [bilirubin, AST (SGOT), ALT (SGPT), and alkaline phosphatase, total protein, albumin].
- Thyroid function tests (TSH, FT4).

**Twice (Week 9, Week 21; these will be performed at the 4th and 8th doses of pembrolizumab, respectively):**

- Anti-thyroglobulin antibody, thyroid peroxidase antibody, thyroid stimulating immunoglobulin, and ANA.

## 8.3 Post-treatment Evaluations

### 8.3.1 Response Assessment

**8.3.1.1 RECIST 1.1. Response assessment by RECIST 1.1 is required; integrated PET/CT interpretation is strongly recommended where available.**

**Twelve to 14 weeks following completion of cisplatin-IMRT (week 20-22 of protocol treatment), patients on both treatment arms will undergo diagnostic contrasted CT scan of the neck and chest, to assess treatment response according to RECIST 1.1. In the case where MRI of the neck was required for baseline tumor measurements, MRI of the neck should be repeated for response assessment, with non-contrasted diagnostic CT of the chest. Note: where available, an integrated PET/CT with contrasted diagnostic CT scans of the neck and chest is strongly preferred for response assessment.**

**8.3.1.2 Evaluation by an otolaryngologist with endoscopy as indicated.**

**8.3.1.3 The patient will be evaluated by the otolaryngologist 12-14 weeks following completion of cisplatin-IMRT (during weeks 20-22).** Endoscopy for oropharyngeal or unknown primary carcinoma will be performed for response assessment as clinically indicated, and is at the discretion of the surgeon. Endoscopy is required for hypopharyngeal and laryngeal carcinoma. The surgeon will evaluate the need for primary site biopsy and/or neck dissection.

### 8.3.2 End of Treatment Visit(s): Week 33 (+/- 2 weeks) for Arm 1; Week 24 (+/- 2 weeks) for Arm 2. Patients will undergo the following procedures at the end of treatment visit:

- History and physical examination and performance status.
- Assessment for resolution of toxicities, including irAE, with attribution.
- Thyroid function testing (TSH, T3, FT4).
- Complete blood count, including platelets and differential.
- Blood chemistries (may be obtained from whole blood or serum/plasma sample), including BUN, creatinine, electrolytes (K+, Na+, CI-, CO2), calcium, Mg++ and liver function tests (bilirubin, AST (SGOT), ALT (SGPT), and alkaline phosphatase, total protein, albumin).
- Audiogram assessment as indicated.

### 8.3.3 Surgical Consolidation

The necessity for and the timing of surgical consolidation will be determined by the surgeon. If patients undergo surgical consolidation, tumor tissue should be submitted for correlative study.

Primary Site

Surgery will be performed in the setting of resectable residual disease if the patient is considered a surgical candidate and:

1) Definitive radiotherapy was not completed, and radiographic or clinical evidence of persistent or progressive disease is established.

2) Biopsy-proven disease is demonstrated at the primary site and/or neck at least 8-12 weeks after completion of IMRT. In cases of residual disease at the primary site, the neck will always be dissected at the time of surgical salvage (if neck dissection was not previously conducted at post-protocol biopsy).

Surgical Management of the Neck

Neck dissection will be performed, if there is concern for residual disease. The extent of neck dissection will be determined by the surgeon. The consideration to perform less than radical procedures is strongly encouraged if oncologically safe. Note: the presence of residual disease at surgical consolidation, if performed within 24 weeks of completion of IMRT, will not constitute a progression event.

## 8.4 Long Term Follow Up

After the end of treatment visit, patients will be evaluated every 3 months for 21 months (+/- 2 weeks), then every 6 months (+/- 1 month) for one year, then annually (+/- 1 month) for two years, which will represent a total of 5 years from completion of IMRT. Thus, long-term follow-up evaluations will start approximately 6 months after completion of IMRT, and will include the following:

- History and physical examination and performance status.
- Vitals signs, including weight.
- Assessment for late toxicity, including dysphagia, xerostomia, gastrostomy tube dependence, pain, fibrosis and lymphedema within the head and neck, hypothyroidism, late autoimmune events.
- Thyroid function testing (TSH, FT4).
- Complete blood count, including platelets and differential.
- Blood chemistries (may be obtained from whole blood or serum/plasma sample), including BUN, creatinine, electrolytes (K+, Na+, CI-, CO2), calcium, Mg++ and liver function tests (bilirubin, AST (SGOT), ALT (SGPT), and alkaline phosphatase, total protein, albumin)
- During the long term follow-up period, tumor assessments will be performed 6, 9, 12, 18, 24, 36, 48, and 60 months after completion of radiotherapy (+/- one month). The minimum protocol imaging requirement is: contrasted, diagnostic neck and chest CT at intervals specified above. More intensive imaging may be conducted per local practice.
- Swallowing assessments per local practice and as indicated by post-radiotherapy evaluation and patient-reported symptoms.
- Note: patients who have documented progression may discontinue scheduled study assessments and will be followed only for survival. Survival assessments will be performed every 6 months (+/- 2 months) by telephone contact and/or by evaluation of the Social Security Death Index or other public records.

# 9. STATISTICAL METHODS

This is a randomized, parallel group, non-comparative phase II trial evaluating the safety and efficacy of two schedules of fixed-dose pembrolizumab combined with standard cisplatin-IMRT in intermediate or high risk, PULA HNSCC: sequential and concurrent. This study is being performed in order to provide: a) necessary safety experience; b) preliminary efficacy estimates; c) characterization of the PD-L1 biomarker in the context of definitive chemoradiation; d) the recommended schedule for definitive testing.

### *Primary Objective*

To evaluate two schedules of fixed-dose pembrolizumab (concurrent vs. sequential) added to standard, concurrent cisplatin-IMRT in patients with PULA HNSCC, in order to recommend the schedule to be tested in a subsequent definitive, randomized study.

### *Sample Size Determination*

The target sample size is 40 evaluable patients per arm. Assuming 10% drop out or ineligibility, 90 patients will be randomized (all evaluable patients will be analyzed). The sample size is determined based upon the following assumptions: 1) the 1-year PFS in the high risk population treated with conventional cisplatin-radiotherapy is 60%;[6] 2) As defined, DLTs occurring in more than 20% of the study population are unacceptable and would constitute an unsafe regimen; 3) The study requires adequate power to detect a signal of antagonism, defined as a 1-year local failure rate

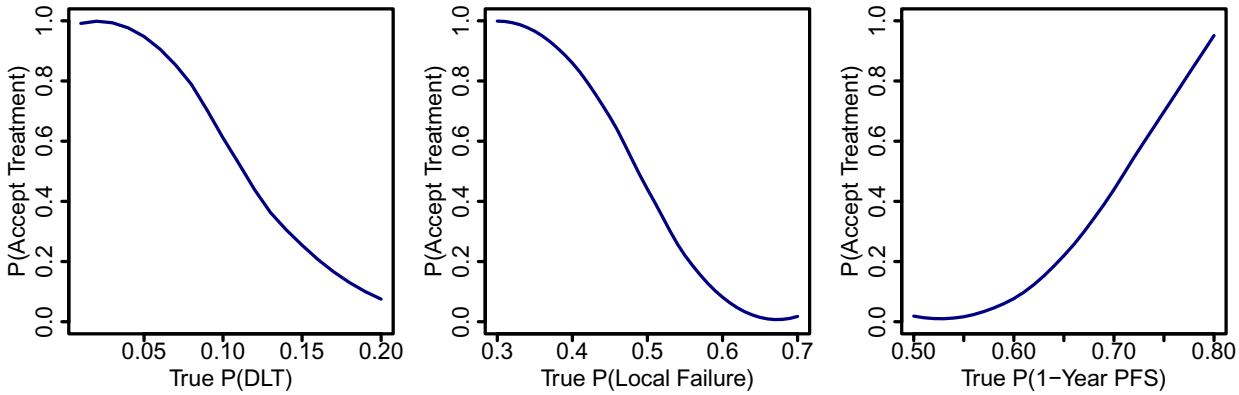
exceeding 60%. To advance to Phase II/III testing, a treatment arm must meet all of the following criteria:

- DLT occurs in ≤ 20%
- 1-year local failure rate is < 60%
- 1-year PFS is ≥ 60%

If both arms meet the above criteria, then the treatment arm demonstrating numerically superior 1-year PFS will advance for definitive testing, as in a so-called "pick-the-winner" trial model. An early phase trial cannot provide the statistical power required for a formal statistical comparison between arms.

The graphic in Figure 1 below demonstrates the probability of accepting either treatment (that is, based on n = 40 evaluable patients per arm) by means of 90% one-sided exact confidence intervals (CI) for DLT, 1-year failure rate, and 1-year PFS. If the upper bound of the DLT CI is less than 0.20, the upper bound of the failure CI is less than 0.60, and the lower bound of the 1-year PFS CI is greater than 0.60, the treatment will be accepted.

**Figure 1: Probability of accepting the treatment according to the three primary metrics**




*Early Stopping Rule*

Dose Limiting Toxicity (DLT; see Section 5.8 for DLT definition) will be continuously monitored in both treatment arms, and is explicitly intended for the purposes of safety monitoring of the concurrent combination of pembrolizumab and cisplatin-IMRT (Arm 2). As defined, excess DLT is not expected during standard of care cisplatin-IMRT. Excess DLT in either arm, however, would trigger the early stopping rule. A continuous Bayesian stopping rule will be adopted, once 4 patients have accrued to either treatment arm. For either arm, if p(p(DLT)>0.2) ≥ 0.6, then the stopping rule would be triggered. Table 11 describes the number of DLTs per number of treated patients required to trigger the early stopping rule, which will require a suspension of accrual to that Arm and evaluation of toxicity data by the H&N Program DSMC to determine further action.

Table 11. Boundaries for the Early Stopping Rule for Excess DLT

| | Number of patients treated on that Arm |
|---|---|

| | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 | 36 |
|---|---|---|---|---|---|---|---|---|---|
| Accrual to the arm is halted if the number of DLTs is greater than or equal to | 2 | 3 | 4 | 4 | 5 | 6 | 7 | 8 | 9 |

*Analysis Plan*

The proportions of patients experiencing DLT, local failure at 1 year, or are progression-free at one year will be calculated with exact (Klopper-Pearson) 90% confidence intervals. Adverse events will be tabulated by category and grade. The relationship between the three primary metrics and baseline PD-L1 expression will be assessed using logistic regression.

*Secondary Endpoints*

**Toxicity**

All patients will be evaluable for toxicity from the time of their first treatment with pembrolizumab. The proportion of DLTs in each dosing arm (concurrent vs. sequential) will be reported, as will the proportion of AEs in accordance with NCI CTCAE v.4 grading criteria.

**Preliminary efficacy data**

Overall and progression-free survival in both arms will be characterized by product-limit (Kaplan-Meier) survival function estimates with appropriate confidence intervals. The study is not adequately powered for a formal test comparing PFS between arms.

## 10. LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES 10.1Investigational 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 the investigational product, pembrolizumab, in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by Merck

as summarized in Table 7. Table 12. Product

Descriptions

| Product Name & Potency | Dosage Form |
|---|---|
| Pembrolizumab 50 mg | Lyophilized Powder for Injection |
| Pembrolizumab 100 mg/ 4mL | Solution for Injection |

### 10.2 Packaging and Labeling Information

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

#### Clinical Supplies Disclosure

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

### 10.3Storage 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.

### 10.4Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and

returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

# 11 ASSESSING AND REPORTING ADVERSE EVENTS

## 11.1Definition of Adverse Event

Adverse event means any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related.

Suspected adverse reaction. Any adverse event for which there is a reasonable possibility that the drug caused the adverse event (considered "possibly related"). For the purposes of safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of suspected adverse reactions where there is reason to conclude that the drug caused the event.

Serious Adverse Event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Specifically, results in death, is life-threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Any subject death within 30 days of the last dose of study drug, regardless of the causality or a secondary malignancy should also be recorded as a serious adverse event.

Life-threatening, suspected adverse reaction. A suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator), its occurrence places the patient or research subject at immediate risk of death. It does not include a suspected adverse reaction that had it occurred in a more severe form, might have caused death.

Unexpected, suspected adverse reaction. A suspected adverse reaction is considered “unexpected” if it is not listed in the general investigational plan or clinical protocol; or is not listed at the specificity or severity that has been previously observed and/or specified. If an investigator brochure is not required or available, suspected adverse reaction is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation. Any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure can also be considered unexpected. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

All observed or volunteered adverse events (serious or non-serious) and abnormal test findings, regardless of study group or suspected causal relationship to the study drug(s) will be recorded in the subjects’ case histories. For all adverse events, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a serious adverse event) and; 2) an assessment of the casual relationship between the adverse event and the study drug(s). All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria version 4.0.

Adverse events or abnormal test findings felt to be associated with the study drug(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Principal Investigator.

In the event of an adverse event the first concern will be for the safety of the subject.

**11.2 Review of safety information. The principal investigator / sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States. The study sponsor must notify all**

**participating investigators of potential serious risks, from clinical trials or any other source, as soon as possible. Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck.**

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

If a dose of pembrolizumab 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 within 24 hours to the Sponsor and within 2 working days to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215 993-1220) using the departmental SAE form or on a Form FDA 3500 MedWatch.

### 11.3 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

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 or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant 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 and within 2 working days to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215 993-1220) using the departmental SAE form or on a Form FDA 3500 MedWatch.

## 11.4 Immediate Reporting of Adverse Events to the Sponsor, Institutional IRB, and to Merck

### 12.4.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any time during protocol treatment with pembrolizumab, cisplatin and IMRT that:

- Results in death.
- Is life threatening.
- Results in persistent or significant disability/incapacity.
- Results in or prolongs an existing inpatient hospitalization (NOTE: Elective outpatient procedures for feeding tube placement do not constitute SAEs in this protocol.)
- Is a congenital anomaly/birth defect.
- Is a new cancer (that is not a condition of the study).
- Is associated with an overdose.
- Is another important medical event.

Refer to Table 13 below 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 that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety using the departmental SAE form or on a Form FDA 3500 MedWatch 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 treatment, or 30 days following cessation of 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 whether or not related to pembrolizumab, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety using the departmental SAE form or on a Form FDA 3500 MedWatch. Elective outpatient procedures for feeding tube placement do not require expedited Adverse Event Reporting.

Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to pembrolizumab 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 and to Merck Global Safety using the departmental SAE form or on a Form FDA 3500 MedWatch.

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

**SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215- 993-1220**

### 12.4.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215 993-1220) using the departmental SAE form or on a Form FDA 3500 MedWatch.

For the time period beginning when the consent form is signed 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 and within 2 working days to Merck Global Safety 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, or placebo treatment.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

1. An overdose of pembrolizumab, as defined in Section 12.2 - 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.

### 12.4.3 Evaluating Adverse Events

**Table 13. 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 mid symptoms; clinical or diagnostic observations only; intervention not indicated.** |
| | **Grade 2** | **Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.** |
| | **Grade 3** | **Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.** |
| | **Grade 4** | **Life threatening consequences; urgent intervention indicated.** |
| | **Grade 5** | **Death related to AE** |
| **Seriousness** | A serious adverse event is any adverse event occurring at any dose or during any use of pembrolizumab 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 [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.. Moreover, Elective hospitalization for feeding tube placement does not constitute a serious adverse event); 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) **or** | |
| | **Is an overdose** (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. 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 Merck product to be discontinued? | |
| **Relationship to pembrolizumab, cisplatin, and/or IMRT** | Did the pembrolizumab cause the adverse event? The determination of the likelihood that pembrolizumab 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 pembrolizumab and the adverse event based upon the available information. The physician will also take into consideration the relationship of the adverse event to the standard study treatments, cisplatin and IMRT.<br>**The following components are to be used to assess the relationship between pembrolizumab and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the pembrolizumab caused the adverse event (AE): | |

| | | |
|---|---|---|
| | **Exposure** | Is there evidence that the subject was actually exposed to the Merck 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 pembrolizumab?<br>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)//cisplatin/IMRT, or other host or environmental factors |

| | | |
|---|---|---|
| **Relationship to pembrolizumabm cisplatin, and/or IMRT (continued)** | **The following components are to be used to assess the relationship between the test drug and the AE: (continued)** | |
| | **Dechallenge** | Was the Merck product discontinued or dose/exposure/frequency reduced?<br>If yes, did the AE resolve or improve?<br>If yes, this is a positive dechallenge. If no, this is a negative dechallenge.<br>(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 Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.) |
| | **Rechallenge** | Was the subject re-exposed to pembrolizumab in this study?<br>If yes, did the AE recur or worsen?<br>If yes, this is a positive rechallenge. If no, this is a negative rechallenge.<br>(Note: This criterion is not applicable if the initial AE resulted in death or permanent disability.<br>NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY PEMBROLIZUMAB, OR IF REEXPOSURE TO PEMBROLIZUMAB POSES ADDITIONAL POTENTIAL SIGNIFICANT<br>RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE PRINCIPAL INVESTIGATOR 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 pembrolizumab 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 pembrolizumab relationship).** | |
| **Yes, there is a reasonable possibility of pembrolizumab relationship.** | There is evidence of exposure to pembrolizumab. The temporal sequence of the AE onset relative to the administration of pembrolizumab is reasonable. The AE is more likely explained by pembrolizumab than by another cause. | |
| **No, there is not a reasonable possibility of pembrolizumab relationship** | Subject did not receive pembrolizumab OR temporal sequence of the AE onset relative to administration of pembrolizumab is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.) | |

Timelines for Reporting of Suspected Adverse Events

In the event of a serious adverse event, the principal investigator, the University of Pittsburgh Institutional Review Board, and as applicable the local institutional review board (per institutional reporting requirements), and Merck will be notified using the the departmental SAE form or FDA Form 3500 MedWatch.

All events meeting the definition of a serious adverse event should be recorded on the departmental SAE form or on a Form FDA 3500 MedWatch (http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf) and submitted to:

Sponsor-Investigator (Principal Investigator) – within 24 hours of the Investigator learning of th event

David Clump MD
c/o UPCI Clinical Research Services
UPMC Cancer Pavilion
5150 Centre Ave., Suite 301
Pittsburgh, PA 15232-1305
Phone 412-623-6096
Fax 412-623-0004
crssafetysubmissions@upmc.edu

Local Institutional Review Board – timeline per institutional reporting requirements

Merck Global Safety (Attn: Worldwide Product Safety; FAX 215 993-1220) – within 2 working days of the Investigator learning of the event

In addition to completing appropriate patient demographic and suspect medication information, the report should include as applicable the following information that is available at the time of report within the Narrative (Section C) on the departmental SAE form or the Event Description (section 5) of the Form FDA 3500 MedWatch:

- CTCAE term(s) and grade(s).
- current status of study drug.
- all interventions to address the AE (testing and result, treatment and response).
- hospitalization and/or discharge dates.
- event relationship to study drug.

Follow-up reports:

Additional information may be added to a previously submitted report by adding to the original departmental SAE form or the Form FDA 3500 MedWatch and submitting it as follow-up or creating supplemental summary information and submitting it as follow-up with the original MedWatch 3500 form. Data Safety and Monitoring Plan

The study will be monitored by the UPCI/UPMC Data Safety and Monitoring Committee (DSMC). In addition, Investigator/Sub-investigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet monthly in the head and neck cancer disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, the following:

- serious adverse events
- subject safety issues
- recruitment issues
- accrual
- protocol deviations
- unanticipated problems
- breaches of confidentiality

All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria version 4.0. All study treatment associated adverse events that are serious, at least possibly related and unexpected will be reported to the IRB. Any modifications necessary to ensure subject safety and decisions to continue, or close the trial to accrual are also discussed during these meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the IRB will be notified in the form of an Unanticipated Problem submission and the study may be terminated.

All study data reviewed and discussed during these meetings will be kept confidential. Any breach in subject confidentiality will be reported to the IRB in the form of an Unanticipated Problem submission. The summaries of these meetings are forwarded to the UPCI DSMC which also meets monthly following a designated format.

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events). DSMC progress reports, to include a summary of all serious adverse events and modifications, and approval will be submitted to the IRB at the time of renewal.

Protocols with subjects in long-term (survival) follow-up or protocols in data analysis only, will be reviewed semi-annually.

Both the UPCI DSMC as well as the individual disease center DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these meetings.

All records related to this research study will be stored in a locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records.

# 13. ADMINISTRATIVE AND REGULATORY DETAILS

## 13.1 Quality Control and Quality Assurance

Independent monitoring of the clinical study for protocol and GCP compliance will be conducted periodically (i.e., at a minimum of annually) by qualified staff of the Education and Compliance Office – Human Subject Research, Research Conduct and Compliance Office, University of Pittsburgh.

The Sponsor-Investigator and the University of Pittsburgh and UPMC will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

## 13.2 Data Handling and Record Keeping

The Sponsor-Investigator will maintain records in accordance with Good Clinical Practice guidelines.

The Sponsor-Investigator will retain the specified records and reports for up to 2 years after the marketing application is approved for the investigational drug; or, if a marketing application is not submitted or approved for the investigational drug, until 2 years after investigations under the IND have been discontinued and the FDA so notified.

## 13.3 Ethics

### 13.3.1 Institutional Review Board (IRB) approval

The Sponsor-Investigator will obtain, from the University of Pittsburgh Institutional Review Board (IRB), prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the Sponsor-Investigator will promptly notify the University of Pittsburgh IRB of the deviation.

The University of Pittsburgh IRB operates in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (CGP).

In the event of the Sponsor-Investigator's decision to modify the previously accepted clinical protocol:

- For Phase 2 and 3 clinical studies: The Sponsor-Investigator will submit (i.e., in advance of implementing the change) a Protocol Amendment to the IRB describing any change to a Phase 2 or Phase 3 protocol that significantly affects the safety of subjects, the scope of the investigation,

or the scientific quality of the study. Examples of Phase 2 and 3 clinical protocol changes requiring the submission of a Protocol Amendment include:

- Any increase in drug dosage or duration of exposure of individual subjects to the investigational drug beyond that described in the current protocol, or any significant increase in the number of subjects under study.
- Any significant change in the design of the protocol (such as the addition or deletion of a control group).
- The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor the safety of the investigational drug.

### 13.3.2 Ethical and scientific conduct of the clinical research study

The clinical research study will be conducted in accordance with the current IRB-approved clinical protocol; ICH GCP Guidelines adopted by the FDA; and relevant policies, requirements, and regulations of the University of Pittsburgh IRB, University of Pittsburgh and UPMC, Commonwealth of Pennsylvania, and applicable federal agencies.

### 13.3.3 Subject Informed Consent

The Sponsor-Investigator will make certain that an appropriate informed consent process is in place to ensure that potential research subjects, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research subjects. The Sponsor-Investigator, or a sub-investigator(s) designated by the Sponsor-Investigator, will obtain the written, signed informed consent of each subject, or the subject's authorized representative, prior to performing any study-specific procedures on the subject. The date and time that the subject, or the subject's authorized representative, signs the informed consent form and a narrative of the issues discussed during the informed consent process will be documented in the subject's case history. The Sponsor-Investigator will retain the original copy of the signed informed consent form, and a copy will be provided to the subject, or to the subject's authorized representative.

The Sponsor-Investigator will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled subjects are adequately addressed and that the subjects are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the Sponsor-Investigator will obtain the informed consent of enrolled subjects for continued participation in the clinical study.

## 13.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. 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.

# 14. LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

## 14.1Investigational 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 the investigational product, pembrolizumab, in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by Merck as summarized in Table 12.

## 14.2 Packaging and Labeling Information

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

## 14.3 Clinical Supplies Disclosure

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

## 14.4 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.

## 14.5 Returns and Reconciliation

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

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator’s responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

## 15. APPENDICES

## APPENDIX A: TOBACCO USE ASSESSMENT FORM

1. Have you ever smoked a total of 100 cigarettes (approximately 5 packs) or more over your life-time?

   ○ Yes ○ No

2. Have you ever smoked cigarettes regularly, that is, at least one cigarette per day for six months or longer?

   ○ Yes ○ No

3. How old were you when you first started smoking at least one cigarette per day?

   _____years old

4. Do you currently smoke cigarettes?

   ○ Yes ○ No

   If no, how old were you when you last smoked a cigarette?

   _____years old

5. Thinking about all the years that you have smoked, how many cigarettes do you (or did you) usually smoke in a day?

   ○ 1-9 cigarettes per day

   ○ 10 to 19 cigarettes per day

   ○ 20 to 29 cigarettes per day

   ○ 30 to 39 cigarettes per day

   ○ 40 to 49 cigarettes per day

6. Have you ever smoked cigars regularly, that is, at least one cigar per day for six months or longer?

   ○ Yes ○ No

7. How old were you when you first started smoking at least one cigar per day?

   _____years old

8. Do you currently smoke cigars?

   ○ Yes ○ No

   If no, how old were you when you last smoked a cigar?

   _____years old

9. How many cigars did you usually smoke in a day?

   _____cigars per day

10. Have you ever smoked a pipe regularly, that is, at least one pipe per day for six months or longer?

    ○ Yes ○ No

11. How old were you when you first started smoking at least one pipe per day?

    _____years old

12. Do you currently smoke a pipe?

    ○ Yes ○ No

    If no, how old were you when you last smoked a pipe?

    _____years old

13. Thinking about all the years that you have smoked, how many pipes do you (or did you) usually smoke in a day?

    _____pipes per day

## APPENDIX B: PERFORMANCE STATUS CRITERIA

| ECOG Performance Status Scale | | Karnofsky Performance Scale | |
|---|---|---|---|
| Grade | Descriptions | Percent | Description |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. | 100 | Normal, no complaints, no evidence of disease. |
| | | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work). | 80 | Normal activity with effort; some signs or symptoms of disease. |
| | | 70 | Cares for self, unable to carry on normal activity or to do active work. |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. | 60 | Requires occasional assistance, but is able to care for most of his/her needs. |
| | | 50 | Requires considerable assistance and frequent medical care. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. | 40 | Disabled, requires special care and assistance. |
| | | 30 | Severely disabled, hospitalization indicated. Death not imminent. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | 20 | Very sick, hospitalization indicated. Death not imminent. |
| | | 10 | Moribund, fatal processes progressing rapidly. |
| 5 | Dead. | 0 | Dead. |

## APPENDIX C: Study Calendars

## Arm 1:

| | | Study Treatment (weeks) | | | | | | | | | | | | | | | Post -tx | Long Term Follow Up[m] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pre-study[a] | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 9 | 12 | 15 | 18 | 21 | 24 | 27 | 30 | 33 +/- 2 | (at 6, 9, 12, 18, 24, 36, 48, 60 months) |
| Medical History, PE, Vital Signs | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Height | x | | | | | | | | | | | | | | | | | |
| Weight | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| ECOG PS | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| CBC with Differential [b] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Blood chemistry[c] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Liver function[d] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Concomitant meds | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Pregnancy test[n] | x | | | | | | | | | | | | | | | | | |
| Oropharyngeal cases, p16 status[0] | x | | | | | | | | | | | | | | | | | |
| Thyroid function[e] | x | | | x | | | x | | x | x | x | x | x | x | x | x | x | x |
| ANA, anti-Tg Ab, TPO, TSI[r] | x | | | | | | x | | | | | x | | | | x | | |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ENT/endo-scopy evaluation[p] | x | | | | | | | | | | | | x | | | | | |
| Tobacco history | x | | | | | | | | | | | | | | | | | |
| Tumor measurements, RECIST[f] | x | | | | | | | | | | | | x | | | | x | x |
| PET/CT[g] | x | | | | | | | | | | | | x | | | | x | x |
| CT neck[h] | x | | | | | | | | | | | | x | | | | x | x |
| CT chest[i] | x | | | | | | | | | | | | x | | | | x | x |
| Dental evaluation[j] | x | | | | | | | | | | | | | | | | | |
| Nutrition consult[j] | x | | | | | | | | | | | | | | | | | |
| SLP consult[j] | x | | | | | | | | | | | | | | | | x | x |
| Audiogram[j] | x | | | | | | | | | | | | | | | | x | x |
| Cisplatin[q] | | x | x | x | x | x | x | x | | | | | | | | | | |
| Pembrolizumab | | | | | | | | | x | x | x | x | x | x | x | x | | |
| IMRT | | x | x | x | x | x | x | x | | | | | | | | | | |
| Adverse event evaluation | | | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |

Arm 2:

| | | **Study Treatment (weeks)** | | | | | | | | | | | | | **Post-tx** | **Long Term Follow Up[m]** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pre-study | -1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 9 | 12 | 15 | 18 | 21 | 24 +/- 2 | (at 6, 9, 12, 18, 24, 36, 48, 60 months) |
| Medical History, PE, Vital Signs | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Height | x | | | | | | | | | | | | | | | |
| Weight | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| ECOG PS | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| CBC with Differential [b] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Blood chemistry [c] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Liver function[d] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Concomitant meds | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Pregnancy test[n] | x | | | | | | | | | | | | | | | |
| Oropharyngeal cases, p16 status[0] | x | | | | | | | | | | | | | | | |
| Thyroid function[e] | x | | | | x | | | x | | x | x | x | x | x | x | x |
| ANA, anti-Tg Ab, TPO, TSI[r] | x | | | | | | | x | | x | | | | x | | |
| ENT/endo-scopy evaluation[p] | x | | | | | | | | | | | | | | | |
| Tobacco | x | | | | | | | | | | | | | | | |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| history | | | | | | | | | | | | | | | | |
| Tumor measurements, RECIST[f] | x | | | | | | | | | | | | | | | x |
| PET/CT[g] | x | | | | | | | | | | | | | | | x |
| CT neck[h] | x | | | | | | | | | | | | | | | x |
| CT chest[i] | x | | | | | | | | | | | | | | | x |
| Dental evaluation[j] | x | | | | | | | | | | | | | | | |
| Nutrition consult[j] | x | | | | | | | | | | | | | | | |
| SLP consult[j] | x | | | | | | | | | | | | | | | x |
| Audiogram[j] | x | | | | | | | | | | | | | | | x |
| Cisplatin[q] | | | x | x | x | x | x | x | x | | | | | | | |
| Pembrolizumab | | x | | | x | | | x | | x | x | x | x | x | | |
| IMRT | | | x | x | x | x | x | x | x | | | | | | | |
| Adverse event evaluation | | | x | x | x | x | x | x | x | x | x | x | x | x | x | x |

a. Pre-treatment evaluations will be performed within 4 weeks prior to registration, unless otherwise specified.

b. Complete blood count with differential (CBCDs) should include WBC, ANC, PLT, Hb, Hct. CBCDs required for protocol therapy may be performed on the day of or the day prior to cisplatin/pembrolizumab administration.

c. Blood chemistry should include Na, K, Cl, $CO_2$, BUN, Cr, Glucose, Ca and Magnesium and be either Serum or Whole blood based on institutional practices/policies.

d. Liver function tests should include SGOT (AST), SGPT (ALT), total bilirubin, total protein, albumin, alkaline phosphatase.

e. Thyroid function studies (TSH, FT4) are required at baseline, and at weeks 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, and recommended at week 33 f/u (Arm 1); TSH, FT4 is required at baseline, and at weeks 3, 6, 9, 12, 15, 18, and 21 and recommended at week 24 f/u (Arm 2). TSH and FT4 are required at 6, 9, 12, 18, 24, 36, 48, and 60 month follow-up in both Arms.

f. A diagnostic contrast CT of the neck and chest will be conducted for staging and tumor measurements at baseline, and 12-14 weeks after completing IMRT. If feasible at participating sites, an integrated PET/CT with diagnostic contrasted CT is recommended at both time points. Tumor measurements will be conducted in accordance with RECIST 1.1. Rare patients may require an MRI for tumor measurements, due to allergy to iodinated contrast despite premedication. In these patients, MRI of the neck should be performed at baseline and at first response assessment. During long term f/u, neck MRI should continue to be performed in the place of neck CT.

g. Integrated PET/CT with diagnostic contrasted neck CT is strongly recommended at pre-study baseline and 12-14 weeks after completing IMRT. However, PET/CT is not required for study participation.

h. CT of the neck (or MRI in those with iodinated contrast allergy) will be conducted at the following intervals post IMRT: 6 mos, 9 mos, 12 mos, 18 mos, 24 mos. More intensive imaging may be conducted per local practice.

i. Chest CT (without contrast in those with iodinated contrast allergy) will be conducted at the following intervals post IMRT: 6 mos, 9 mos, 12 mos, 18 mos, 24 mos.

j. These evaluations are strongly encouraged, but not mandatory. See section 5.4.13 for guidelines.

k. Long term follow up assessments (examination, non-thyroid laboratories, adverse event/late toxicity assessments) should occur every 3 months for 2 years, then every 6 months for 3 years, for a total of 5 years from completion of IMRT. No specific requirements if patient is more than 5 years from study entry. If patient dies during follow-up, cause of death should be recorded.

l. Women of child bearing potential are required to have a pregnancy test within 2 weeks of 1$^{st}$ study treatment to rule out pregnancy

m. For oropharyngeal cases, p16 status must be established at the participating site, if not previously known before the screening process.

n. Evaluation by an otolaryngologist with endoscopy. Endoscopy is not required for oral cavity carcinoma. Endoscopy for oropharyngeal carcinoma may be performed as clinically indicated. Endoscopy is required for hypopharyngeal and laryngeal carcinoma.

o. Cisplatin should be administered on Monday, Tuesday, or Wednesday of each treatment week and may be given either before or after the radiation therapy fraction that is given on the same day. When cisplatin and pembrolizumab are administered on the same day in Arm 2, pembrolizumab should follow cisplatin.

p. Thyroid auto-immunity will be monitored as specified in section 8.2.

**APPENDIX D: CTCAE v.4.0**

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

## APPENDIX E: MEDWATCH FORM 3500A

http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/ucm082728.pdf

## 16. REFERENCES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# DNA/RNA Shield™ Fecal Collection Tube

Catalog No. R1100-9-T

## Quick Protocol

ZYMO RESEARCH

*The Beauty of Science is to Make Things Simple*

**Description**

The DNA/RNA Shield™ Fecal Collection Tube ensures sample stability during storage/transport at ambient temperatures without the need for refrigeration or specialized equipment. DNA/RNA Shield™ reagent effectively lyses samples and inactivates pathogens (e.g., virus, bacteria).

Each collection tube (with a spoon attached to the cap) is pre-filled with DNA/RNA Shield™ (9 mL). The nucleic acids (DNA & RNA) in samples are preserved at ambient temperature (DNA >1 year, RNA up to 1 month). Samples in the DNA/RNA Shield™ can be frozen (-20/-80°C) for prolonged storage.

**Required Fecal Collection Accessories (Not included)**

1. Fecal specimen collector set (e.g., hat-style specimen collector)
2. Labels for identification of samples
3. Appropriate waste container/biological waste container

**Instructions**

1. Prepare and collect fecal specimen using preferred fecal specimen collection set/kit.

   Note: Method of collecting the fecal sample must prevent feces from falling into toilet water to avoid sample contamination.
2. Unscrew the collection tube cap and use the spoon to scoop **one spoonful** of feces (approximately 1 gram or 1 mL in volume) from a sample.
3. Place the sample in the collection tube.
4. Tighten the cap and shake to mix the contents thoroughly (invert 10 times) to create a suspension.

   Note: Some fecal material may be difficult to re-suspend. As long as the material is suspended, the sample is stabilized. foaming/frothing during shaking is normal.
5. Dispose of unused fecal material and thoroughly wash hands according to your institution's guidelines.

**Sample Purification**

Samples in DNA/RNA Shield™ can be input directly into Zymo Research's (and others) nucleic acid purification kits.

Don't let the sample go into the toilet

Collect stool into a clean container

Scoop a portion of the stool sample into the DNA/RNA Shield™ Fecal Collection Tube

Wash hands well