SPONSOR: University of Cincinnati

TITLE: A Phase I/ II Study of chemo radiation plus the Anti-PD-1 Antibody, Pembrolizumab (MK-3475) for Locally Advanced Laryngeal Squamous Cell Carcinoma

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EudraCT NUMBER (Studies in Europe only):

Principal Investigator:
Vinita Takiar, MD
University of Cincinnati
Barret Center, ML 0757
234 Goodman St.
Cincinnati, Ohio, 45219
Tel: 513-584-5327, Fax: 513-584-5680
Email: takiarva@ucmail.uc.edu

Sub-Investigators (alphabetic order)
David Adelstein, MD
Mustapha Bahassi, PhD
William Barrett, MD
Neal Dunlap, MD
Bradley Huth, MD
Tahir Latif, MD
Jonathan Mark, MD
John Morris, MD
Yash Patil, MD
Kevin Redmond, MD
Keith Wilson, MD
Cristina Rodriguez, MD
Ammar Sukari, MD
Vinita Takiar, MD, PhD
Trisha Wise-Draper, MD, PhD

Biostatistics:
Lisa Rybicki, MS

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1.0 TRIAL SUMMARY

Abbreviated Title	MK-3475 in larynx cancer
Trial Phase	Phase I/II
Clinical Indication	Locally advanced stage III and IV larynx cancer
Trial Type	Open label single arm study
Type of control	None
Route of administration	IV
Trial Blinding	None
Treatment Groups	Single Arm Combination study
Number of trial subjects	47
Estimated enrollment period	18 months
Estimated duration of trial	24 months
Duration of Participation	24 months

2.0 TRIAL DESIGN

2.1 Trial Design

This study is an open label, single arm study which will enroll patients with locally advanced squamous cell carcinomas of the larynx. Positive tumor PDL1 expression by IHC will not be required for enrollment.

All patients with receive Pembrolizumab and cisplatin in combination with radiation. Pembrolizumab 200 mg flat dose given Q21 days will begin 3 weeks prior to initiation of chemoradiation and continued through the 21-day cycle until completion of chemoradiation. Cisplatin will be given 100 mg/m2 every 21 days during radiation as per standard of care.

Pembrolizumab has well defined toxicities as single agent and has non-overlapping mechanisms of action with cisplatin and radiation. The safety of these agents used in combination has not been previously described, therefore the study will begin with a safety run-in phase 1 followed by the phase II design. See statistical section for details.

2.1.1 Phase I run in

Both drugs are FDA approved for other disease indications, with safety and tolerability well described at the approved doses. Therefore the limited phase I portion of this study aims to assess the safety and tolerability of this drug combination at their established doses along with concurrent radiation. There will be no dose escalation cohorts within this phase I run in group.

The first six patients will constitute the phase I portion of this study. These initial 6 patients will be assessed for dose limiting toxicities (DLTs, defined in Section 2.1.1.1)

from the start of study treatment until the start of cycle #2 concurrent cisplatin/radiation and pembrolizumab After these first 6 patients initiate cycle #1, enrollment to the study will be temporarily halted, and a formal DLT evaluation of all 6 patients will be conducted.

If ≤ 2 of these six patients experience DLTs after completion of cycle #1 concurrent cisplain/radiation and Pembrolizumab, then the study will proceed to the phase II portion, using Pembrolizumab 200mg IV Q21 days and cisplatin 100mg IV each 21 day cycle.

If > 2 of these first 6 patients experience a DLT upon completion of cycle #1, the protocol will be amended to investigate use of pembrolizumab 200 mg IV Q 21 days subsequent to completion of chemoradiation. (3-6 weeks after last dose of radiation) (upon Merck approval)

Only upon completion of the DLT evaluation for these first 6 patients and the determination of appropriate Phase II dose, will enrollment reopen for the phase II expansion.

If toxicity results are unclear, we will allow 6 additional patients into Phase I portion (6 + 6) The second cohort will be assessed based on above definitions for DLTs. Unclear toxicity can include (but not limited to) adverse effects that are considered secondary to cisplatin or radiation and per protocol are not considered DLT (see section 2.1.1.1 for definition of DLT) , however, the investigator strongly feels they could be related to study drug or exacerbated by concurrent use of study drug and chemoradiation. This investigator initiated study will be under the oversight of the University of Cincinnati IRB and Data and Safety Monitoring committee.

2.1.1.1 Definition of Dose-Limiting Toxicities

All toxicities will be graded using National Cancer Institute (NCI) CTCAE Version 4.0 (see Appendix).

Dose limiting toxicity (DLT) is defined as the appearance of side effects during treatment that are severe enough to prevent continuation of planned treatment. Dose limiting toxicity is defined as grade 3 or 4 non-hematologic toxicities that is definitely, probably, or possibly related to study drug, excluding alopecia, nausea or vomiting, grade 3 tumor flare, rash, mucositis, radiation dermatitis, need for feeding tube, and grade 3 immune-related events that resolve to grade 1 or less within 28 days. However, Grade ≥3immune-mediated adverse events that include pneumonitis, renal failure nephritis, and elevation of AST, ALT, or bilirubin (with an exception for patients with liver metastases with baseline Grade 2 AST or ALT) should result in discontinuation of pembrolizumab and will be considered DLT (please see Table 3 for details on dose modification) .

In addition, adverse effects that are considered secondary to cisplatin or radiation are not considered DLT (see sections 5.2.1.3 and 5.2.2.7) unless they develop after first dose of pembrolizumab and prior to initiation of cisplatin and radiation. Cisplatin or radiation adverse effects include (but are not limited to):

- Grade 3 or 4 renal impairment (with the exception of renal failure or nephritis determined to be immune-related, which will be considered a DLT).
- Grade 2-4 neurotoxicity including ototoxicity (with the exception of myasthenia gravis and Guillain-Barre syndrome, which will be considered a DLT).
- Grade 3 or 4 mucositis
- Grade 3 or 4 myelosuppression

Although the above should result in dose modifications or delays as stated in section 5.2.1.3, they will NOT be considered DLTs for pembrolizumab on this study, and will NOT interfere with expansion to phase II portion of study.
If a patient is taken off study due to the above and has not yet reached evaluation for toxicity attributed to pembrolizumab, that subject will be replaced with another patient on study.

Non hematologic toxicities that will be attributed to pembrolizumab include:

- Grade 3-4 Pneumonitis
- Grade 3-4 diarrhea/colitis
- Grade 3-4 hyperglycemia
- Grade 3-4 hypophysitis
- Grade 3-4 thyroid dysfunction (hypothyroid or hyperthyroid)
- Grade 3-4 hepatic failure (elevation of AST, ALT, Bilirubin)
- Grade 5 toxicity

Any additional grade 3-4 non hematologic toxicity that is judged by the investigator to be possibly, probably or definitely related to study drug administration will be reviewed by study monitor and PI on an individual basis.

Management and dose modifications associated with the above adverse events are outlined in Sections 5.2.1.2 and 5.6.

2.1.2 Phase II expansion

After the first 6 patients have been assessed for DLTs upon completion of cycle 1 of treatment, and the appropriate Cisplatin dose and Pembrolizumab dosing determined

for phase II expansion, an additional 41 patients with locally advanced larynx squamous cell carcinoma will be enrolled in this phase I/II study. The entire cohort will be used to assess the safety and efficacy outcomes of interest. Safety stopping rules will be applied in the event of excessive toxicity leading to inability of patients to receive at least 2 doses of cisplatin and complete radiation therapy. If radiation treatment breaks are required, greater than a 10 day radiation treatment break in 6 or more patients will also initiate early stop for safety evaluation.

Patients will be evaluated 14 weeks after completion of radiation (14 ± 2 week after completion of radiation) with radiographic imaging to assess response to treatment. All imaging will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

After the end of treatment, each patient will be followed for a minimum of 30 days for adverse event monitoring (serious adverse events will be collected for up to 90 days after the end of treatment). Subjects will have post-treatment follow-up for laryngectomy event and survival status for two years.

Participation in this trial will be dependent upon supplying tumor tissue from a formalin-fixed specimen. Newly obtained formalin-fixed specimens are strongly encouraged 14-20 days after first dose of Pembrolizumab prior to initiation of cisplatin and radiation unless clinically deemed unsafe by the treating physician. The specimen will be evaluated for expression status of PD-L1.

2.1.2.1 Safety assessments during the Phase II expansion

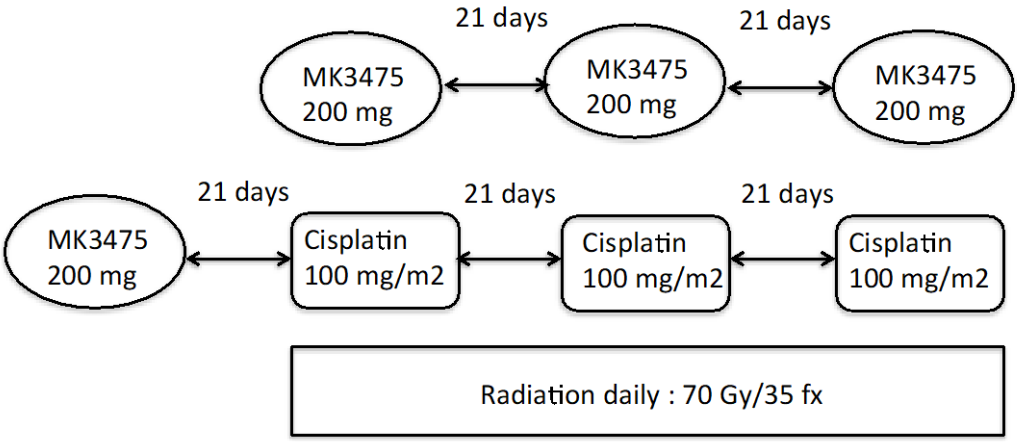
This investigator initiated study will be under the oversight of the University of Cincinnati Cancer Consortium IRB and Data and Safety Monitoring committee. The investigators are ultimately responsible for monitoring the safety of patients who have entered this study and for alerting the Consortium IRB to any event that seems unusual in accordance with IRB policy. The investigator is responsible for the appropriate medical care of patients during the study. The investigator remains responsible to follow, through an appropriate health care option, adverse events that are serious or that caused the patient to discontinue before completing the study. The patient should be followed until the event resolves or stabilizes. Frequency of follow-up is left to the discretion of the investigator.

Safety measurements that will be used in the study include physical examinations and clinical laboratory tests (hematology and blood chemistries). The adverse event will be graded for toxicity using the NCI CTC version 4.0. Toxicity assessment will occur at the start of each cycle, or more frequently if clinically indicated. Any adverse events leading to a treatment interruption or dose reduction along with all adverse events that are grade 3 and higher will be recorded in the CRF.

The criteria for dose de-escalation for adverse events are outlined in Section 5.2. Any patient who requires two dose modifications or de-escalations will be taken off study.

2.2 Trial Diagram

Please refer to timing of treatment administration (section 5.2.1.4) Trial Flow Chart (section 6.0) for details on timing flexibility of treatment administration.



3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

3.1.1 Primary Objective & Hypothesis for phase 1 safety run-in portion:

Objective: Determine the safety and tolerability of **Pembrolizumab** in combination with **cisplatin and radiation** patients with **LA-larynx SCC.**

Hypothesis: The combination of Pembrolizumab with cisplatin and radiation is safe and well tolerated in patients with LA-larynx SCC.

3.1.2 Primary Objective & Hypothesis for phase 2 portion:

(1) **Objective:** Determine the 18-month laryngectomy-free survival in locally advanced laryngeal squamous cell carcinoma (LA-larynx SCC).

Hypothesis: Patients with LA-larynx SCC who receive Pembrolizumab combination with Cisplatin and radiation have a 15% improvement in 18-month laryngectomy-free survival.

3.2 Secondary Objective(s)

(1) **Objective**: Estimate the one-year laryngectomy-free survival in locally advanced laryngeal squamous cell carcinoma (LA-larynx SCC).
(2) **Objective**: Estimate overall survival and progression free survival in patients enrolled in the study
(2) **Objective**: Estimate 3-month complete response rate (CR) in patients enrolled in the study
(3) **Objective**: Estimate event –free survival (events include death, persistent or progressive disease, laryngectomy)

3.3 Exploratory Objective

1. **Objective:** Explore peripheral T cell phenotype at baseline and after treatment with Cisplatin, radiation, and Pembrolizumab.
   Hypothesis: T cell phenotype is altered after exposure to Cisplatin, radiation, and Pembrolizumab, and will correlate with treatment response.
2. **Objective**: Measure expression of the proteins in the PD-1 family on baseline tumor samples and on treatment biopsies.
   Hypothesis: There is a relationship between response to Pembrolizumab and PD-1 protein family expression in both pre- and post-treatment tumor samples. Cisplatin-radiation concurrent with Pembrolizumab impacts the expression of PD-1 family of proteins.
3. **Objective**: Measure circulating tumor DNA in pre-treatment, during treatment, and post-treatment blood samples.
   Hypothesis: There is a relationship between response to Pembrolizumab and circulating tumor DNA level in both pre- and post-treatment tumor samples.
4. **Objective:** Explore Tumor infiltrating immune cell phenotypes and global gene expression (including 12-gene signature) by RNAseq on baseline tumor samples and on treatment biopsies.
   Hypothesis: Tumor infiltrating immune cell phenotypes and global gene expression is altered after exposure to Pembrolizumab, and will correlate with treatment response.
5. **Objective:** Explore patterns of disease recurrence after treatment with Cisplatin, radiation, and Pembrolizumab.
   Hypothesis: Patterns of recurrence of disease is altered after exposure to Pembrolizumab when added to standard Cisplatin and radiation therapy.
6. **Objective:** Explore rates of speech and swallowing dysfunction after completion of treatment with Cisplatin, Radiation, and Pembrolizumab.
   Hypothesis: Rates of speech and swallowing dysfunction is improved after completion of treatment with Cisplatin, Radiation, and Pembrolizumab.
7. **Objective**: Explore PET scan findings after completion of treatment with Cisplatin, Radiation, and Pembrolizumab

Hypothesis: There is a relationship between post treatment PET scan and clinical benefit in patients treated with Cisplatin, Radiation, and Pembrolizumab.

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 Laryngeal cancer

Laryngeal cancer represents one of the more common head and neck malignancies, accounting approximately for 20% of all cases, majority of them (85-90%) being squamous cell carcinomas [1, 2]. Up to 40% of patients present with advanced disease [3]. The term advanced laryngeal cancer generally denotes stage 3 or 4 laryngeal cancers according to the Union for International Cancer Control (UICC) / American Joint Committee on Cancer (AJCC) staging. Since larynx is essential in many physiologic functions including speech production, swallowing, airway protection, and breathing, disruption of any of these functions by either the tumor or the treatment may have devastating consequences for the patient and often associated with significant morbidity and mortality for the patient and a financial costs for society [4, 5]. Therefore, in addition to achieving tumor control, optimizing functional outcomes and organ preservation are very important in treatment of patients with laryngeal carcinoma.

Management of advanced laryngeal cancer is complex and involves different treatment modalities [6]. Total laryngectomy (TL), alone or with neck dissection (ND), radiotherapy (RT) alone, TL followed by RT, and combined chemotherapy and RT (CRT) [6, 7]are considered standard treatment options. Prior to 1991, TL followed by adjuvant RT was widely considered the standard management option [8]. This approach would result in permanent tracheostoma in the neck, alterations in deglutition and loss of natural voice for the patients. The Veterans Administration (VA) study in 1991 sparked a major change in the management of advanced laryngeal cancer. [9]This randomized study involving 332 patients found that induction chemotherapy followed by radiation therapy achieved an equivalent 2 year survival rate (68%) compared with total laryngectomy with postoperative radiation therapy. Moreover, the larynx could be preserved in 64% of patients undergoing chemoradiation therapy. Overall 64% of patients receiving chemoradiation achieved histologically confirmed complete response [9]. No significant difference in survival was reported after more than 10 years of follow up [10]. Patterns of recurrence differed significantly between the two groups with more local recurrences (12% vs 2%) and fewer distant metastases (11% vs 17%) in the chemotherapy group than in the surgery group. Thus addition of chemotherapy to radiation introduced new oncologic end points, namely organ preservation and laryngectomy-free survival (LFS). [9]

The VA study was followed by another landmark study, the Radiation Therapy Oncology Group (RTOG) 91-11 trial reported by Forasteire and colleagues in 2003. This three arm randomized controlled trial in 547 locally advanced (stage III and IV – T2, T3 or low volume T4) resectable laryngeal cancer patients confirmed significantly lower rates of salvage laryngectomies in chemoradiation treated patients. [11]By the end of 2 years, the proportion of alive patients with intact larynx after radiotherapy with concurrent chemotherapy was 88% vs 75% in the group that received induction chemotherapy followed by radiotherapy vs 70% in the radiotherapy group alone, the differences being

statistically significant. Overall survival rates were similar at 75% at 2 years for all treatment groups [11]. In a recent update to the RTOG 91-11 study, composite end point of LFS for the concurrent chemotherapy group was 74% and 63% at 1 and 2 years respectively. AT 10-year follow up, there is no significant difference between the concomitant cisplatin/ RT arm (23.5%) and the induction arm (28.9%). LFS was significantly worse for RT group (17.2%) versus both the induction group and the concomitant group, confirming role of systemic therapy in treatment of laryngeal cancer. [12]
More recent studies that have introduced more aggressive induction chemotherapy regimens [TPF (taxane, cisplatin, and 5-fluorouracil)] to improve on laryngeal preservation rates compared to induction chemotherapy arm of RTOG 91-11 (3-year LFS 70% vs 57%), however, these regimens carry higher adverse events without improvement if PFS or OS. [13]

In the event of locally recurrent, residual disease, or dysfunctional larynx after completion of chemo radiation, salvage laryngectomy is considered standard treatment. However, there appears to be a significantly worse survival outcome for those patients undergoing laryngectomy after patients having been exposed to chemotherapy in combination with radiation [12].

Thus, treatment paradigms for larynx cancer have continued to change since 1991 resulting in variability in the treatment sequence and type of therapeutic modalities used. [14] . Unlike most other malignancies, a recent review of the latest National Cancer Data Base (NCDB) has demonstrated worsening survival outcome of larynx cancer patients in recent years with a 5-year survival at 59% compared to 67 % in 1985. These findings may, to some extent, reflect changes in practice patterns over the last two decades [1]. In addition, some other retrospective studies suggest a possible inferior oncologic outcome in patients who choose organ preservation compared to a more traditional upfront surgery (TL) with 2-year disease specific survival and overall survival (70% vs 64%) and (64% vs 57%) respectively. [15]
These findings suggest a need for further investigation and development of more successful curative organ preservation approaches. Despite multiple trials over the last two decades, overall rates of cure and organ preservation remain suboptimal without much improvement since introduction of concurrent chemo radiation in the landmark RTOG 91-11 study.

4.1.2 Pharmaceutical and Therapeutic Background

4.1.2.1 Pembrolizumab (MK-3475)

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells 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). The structure of murine PD-1 has been resolved. 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. 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. 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. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. 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. 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. 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). 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.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between 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.

4.1.3 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for Preclinical and Clinical data.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

The Programmed death Ligand 1 (PD-L1) / programmed death receptor (PD-1) axis has been identified as an important regulator of the immune system across various solid tumors allowing cancer cells to escape immune response [16]. The normal function of PD -1, an Ig superfamily member related to CD 28 and CTLA-4, expressed on the cell surface of activated T- cells under healthy conditions, is to down modulate unwanted or excessive immune responses, including autoimmune reactions. The ligands for PD-1 (PD- L1 and PD-L2) are constitutively expressed or can be induced in a variety of non-hematopoietic tissues as well as in various tumors. Binding of either PD-1 ligand to PD-1 inhibits T cell activation triggered through the T- cell receptor.

Head and neck squamous cell carcinoma has a prominent immune escape in both HPV positive and negative settings [17, 18]. It has also been shown that in mouse model, blocking PD1/PDL1 interaction can result in tumor regression and survival extension.[19] In addition, it has been shown in pre-clinical models that following radiation, PD-L1 gets up-regulated in the tumor microenvironment and that anti-PD-L1 therapy can improve the efficacy of radiation through a cytotoxic T cell-dependent mechanism, supporting the hypothesis that a PD-L1 / PD-1 inhibitor can restore anti-tumor activity [32].

Pembrolizumab (MK-3475) is a potent and highly selective humanized monoclonal antibody designed to block the interaction between PD-1 and its ligands PD-L1 and PD-L2. It has been shown to have a potent and durable anti-tumor activity in multiple tumor types, including single agent activity in HNSCC [20]. Preliminary data reported in abstract form in 2014 revealed that 78% of RMSCC screened for an ongoing MK-3475 phase Ib study, expressed PD-L1. There have been observations of disease responses in this cohort of 60 patients, many of whom have been heavily pretreated with prior systemic agents[20]. However, combination of Pembrolizumab and chemo radiation has not been examined in humans, which remains important in better understanding of the therapeutic utility of this agent in the vast majority of locally advanced HNSCC. Laryngeal squamous cell carcinoma is unique in the setting for which surgical options are less appealing due to long-term morbidities associated with a total laryngectomy (tracheostomy and loss of voice). Chemo-radiation alone may not be sufficient to avoid surgery and allow for a long-term survival of patients with a functional larynx. This disease is also unique in the setting that it is highly associated with smoking and genetic complexity, making it a favorable target for immune modulators. In addition, biologic correlative testing is feasible due to the accessibility of tumor tissue by biopsy and any specimens from patients undergoing laryngectomy for residual/ progressive or dysfunctioning larynx.

We propose a single arm phase II study to test the hypothesis that the addition of Pembrolizumab to chemoradiation enhances the local effects of standard therapy in laryngeal HNSCC, ultimately allowing for higher rates of functional organ preservation in this population, and leading to improved quality of life. In addition, we hypothesize that adding Pembrolizumab to chemo radiation may result in immune-mediated regression

of micrometastatic disease and lower rates of systemic relapse, similar to what has previously been described in distant untreated melanoma lesions [21] Therefore, we will examine not only laryngectomy-free survival and event-free survival endpoints [including death, persistent disease or progression, laryngectomy (partial or total), and feeding tube dependence], but also pattern of in and out of field tumor growth in these patients. Finally, we will examine exploratory correlative studies that will provide valuable insight into the effects of chemo radiation in combination with PD1 inhibitor on laryngeal carcinoma microenvironment, and the association of tumor response and overall clinical benefit with adaptive PD-L1 tumor expression, immune infiltration, cytokine expression profiles, and genomic signature of tumors. We hypothesize that chemo radiation affects expression of PD1/PD-L1 on tumor infiltrating immune cells detected by IHC and subsequently increases PD-L1 expression on the tumor cells, which will predict response to chemo radiation and PD-1 inhibitor.

We hypothesize by inhibiting PD1 ligands, PDL1 and PDL2, we will activate immune system and allow for better anti-tumor effect, finally resulting in improved laryngectomy-free survival with fewer side effects.

4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent Pembrolizumab (MK-3475). 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 MK-3475 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 MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 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 MK-3475 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. MK-3475 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 MK-3475 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.

4.2.3 Rationale for Endpoints

Cisplatin and pembrolizumab appear to be well tolerated as single agents and have FDA approved doses and indications. These two drugs have non-overlapping mechanisms of action. Cisplatin in combination with radiation is well tolerated and considered standard treatment in laryngeal carcinoma patients who are treated with an organ preservation approach. There has been no reported clinical experience with the combination of cisplatin-radiation and pembrolizumab in locally advanced laryngeal carcinoma patients. Therefore a phase I/II design, wherein a limited phase I run in cohort is initially enrolled, was felt to be most appropriate to study this combination, with laryngectomy-free survival as a composite endpoint to reflect both oncologic and functional outcome as the primary endpoint of interest.

4.2.3.1 Efficacy Endpoints

There is intriguing preclinical and clinical data suggesting that combination of radiation and PD-1 inhibitor can augment the immunologic anti-tumor response to radiation. The

study explores whether chemoradiation combined with a PD-1 inhibitor have synergistic effects, resulting fewer salvage laryngectomies for persistent/ recurrent disease or dysfunctional larynx, and allow for improved quality of life in laryngeal cancer survivors.

Specifically, this study hypothesizes that organ preservation will improve as a consequence of this synergistic effect.

Therefore in addition to above, exploring objective response rates to the combination of pembrolizumab with chemoradiation will be secondary endpoints. Overall survival and progression free survival will be examined as well. If encouraging response rates, and overall and progression free survival are observed in this cohort of patients, further study of the combination in this disease will be justified.

4.2.3.2 Biomarker Research

1. Archived tumor tissue at diagnosis, during treatment tumor biopsies, salvage laryngectomy tissues, and potential biopsies from regional and systemic recurrent disease will be used to examine tumor PD-L1 expression, Tumor infiltrating immune cell phenotypes, global gene expression by RNAseq, and whole genome sequencing in an attempt to define a gene set critical for clinical response to pembrolizumab and chemoradiation and correlate these with clinical benefit and emergence of resistance from combination of Pembrolizumab and chemoradiation.
2. Examine peripheral blood mononuclear cell phenotypes in pre-treatment, during treatment, and post-treatment in blood samples using flow cytometric evaluation of CD3, CD4, CD8, CD14, PD-1, PD-L1, PD-L2, and correlate these with clinical benefit from combination of Pembrolizumab and chemoradiation. In addition to these specific protein biomarkers, both tissue and blood derivatives can be subjected to proteomic profiling studies using a variety of platforms that could include but are not limited to immunoassay, liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab and chemoradiation. Combination therapy.
3. Examine circulating tumor DNA in pre-treatment, during treatment, and post-treatment blood samples, and correlate circulating tumor DNA levels as a potential biomarker for clinical benefit or emergence of early resistance from combination of Pembrolizumab and chemoradiation.
4. Circulating tumor cells (CTCs) hold great promise as a readily available source material that can offer real-time insight into a tumor's genomic architecture. CTCs can be detected in head and neck cancer patients and appear to have prognostic importance. We propose to collect CTCs and assess PD-L1 expression in CTCs and attempt to correlate PD-L1 expression in CTCs with patient's primary tumor and with efficacy parameters.
5. Examine rates of speech and swallowing dysfuncyion after completion of treatment with combination of Pembrolizumab and chemoradiation.
6. Examine correlation of post treatment PET scan findings with clinical benefit in Pembrolizumab treated patients.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Patients with biopsy-proven laryngreal squamous cell carcinoma that are candidates for curative treatment with chemoradiation.

5.1.2 Subject Inclusion Criteria

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

1. Biopsy-proven, previously untreated stage III or IV squamous cell carcinoma of the larynx, Primary tumor stage (T2, T3) and nodal stage (N0,N1,N2,N3).
2. Be willing and able to provide written informed consent/assent for the trial.
3. Be ≥ 18 years of age on day of signing informed consent.
4. Have measurable disease based on RECIST 1.1.
5. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. *Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the Sponsor.*
6. Have a performance status of 0 or 1 on the ECOG Performance Scale.
7. Anticipated survival minimum 12 months.
8. Patient is > 5 years free of another primary malignancy, except: a) if the other malignancy is basal cell carcinoma or cervical carcinoma in situ or b) if the other primary malignancy is not considered clinically significant and is requiring any active intervention

9. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**

	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) 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 ≤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
[a]Creatinine clearance should be calculated per institutional standard.	

10. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
11. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
12. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

5.1.3 Subject Exclusion Criteria

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

1. Patients with T1 primary tumor or T4 large volume tumor that has resulted in larynx dysfunction at baseline (for example tumor largely penetrating into base of tongue and resulting in inability to swallow at baseline)
2. Prior radiation therapy to larynx area or involved neck.
3. Distant metastasis. Small lesions (for example, small nodule in lung) that are not clinically or radiographically suggestive of metastasis do not require biopsy for confirmation.
4. Prior complications from former therapies, such as history of radiation pneumonitis that, in the opinion of the investigator, may have risk of increasing toxicity with anti-PD1 therapy.
5. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.

6. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
7. Has a known history of active TB (Bacillus Tuberculosis)
8. Hypersensitivity to pembrolizumab or any of its excipients.
9. Patients who have not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.
    - Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.
    - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
10. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
11. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
12. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
13. Has known history of, or any evidence of active, non-infectious pneumonitis.
14. Has an active infection requiring systemic therapy.
15. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
16. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
17. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
18. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
19. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
20. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
21. Has received a live vaccine within 30 days of planned start of study therapy.

Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2

Table 2 Trial Treatments

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
pembrolizumab	200 mg	Q3W	IV infusion	Starting 3W (-1 w) prior to chemotherapy, then Day 1 of each 3 week cycle Maximum 4 doses	Experimental
cisplatin	100 mg /m2	Q3W	IV infusion	Day 1 of each 3 week cycle Maximum 3 dose	Standard
radiation	70 Gy/35fx	5 days /W	radiation	7 weeks	Standard

Trial treatment should begin on the day of randomization or as close as possible to the date on which treatment is allocated/assigned.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

Pembrolizumab will be dosed as a flat dose.

Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Pharmacy Manual.

5.2.1.2 Dose Modification for Pembrolizumab

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.6.1 and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids.

Table 3
Dose Modification Guidelines for Pembrolizumab-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 6 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
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 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 6 weeks.
	4	Permanently discontinue	Permanently discontinue
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 6 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.

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 6 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 6 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 6 weeks.
	4	Permanently discontinue	Permanently discontinue

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

[1] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[2] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 6 weeks of the last dose.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

5.2.1.3 Dose Modification for Cisplatin

1. Neutropenia**:** If on the day of scheduled treatment with cisplatin the absolute neutrophil count (ANC) is < 1200/mm3, hold the second chemotherapy treatment but not the radiation until ANC ≥ 1200/mm3, then treat at 100% dose. Neutropenic fever (i.e. any fever > 38.5°C with an ANC <1000/mm3) will require a 25% dose reduction of the next cisplatin dose. If neutropenic fever occurs with both the first and second dose, cisplatin should be discontinued.
2. Thrombocytopenia: If on the day of scheduled treatment with cisplatin the platelet count is < 75,000/mm3, hold chemotherapy treatment but not the radiation until platelets are ≥ 75,000/mm3, then treat at 100% dose. Thrombocytopenia that results in bleeding will require a 25% dose reduction of the following cisplatin dose.
3. Neurotoxicity: If grade 2 neurotoxicity develops, hold cisplatin (but continue RT) until toxicity improves to ≤ grade 1, then reduce the following cisplatin dose to 80 mg/m2. If any signs of grade 3 or greater neurotoxicity occur, discontinue cisplatin, but continue RT.
4. Renal Adverse Events: Cisplatin dose should be based on creatinine clearance immediately prior to the second and third cisplatin dose using the following guidelines:
   Note: Creatinine clearance must be calculated (Cockcroft-Gault) in order to make dose adjustment. If the calculated clearance is 50 mL/min or above, a 24-hour urine collection is not needed, but if the calculation is less than 50 mL/min, a 24-hour urine collection is mandated, and the cisplatin dose will be determined as follows:
   Creatinine Clearance Cisplatin Dose
   > 50 ml/min then administer 100 mg/m2
   40-50 ml/min then administer 50 mg/m2
   < 40 ml/min Hold drug*
   *Cisplatin should be held (but the RT continued) and the creatinine measured weekly, until creatinine clearance is > 50 ml/min, and then the next and following doses of cisplatin should be given at the reduced dose of 50 mg/m2.
5. Nausea and Vomiting: Maximum supportive therapy will be given, and cisplatin will be continued at full dose for ≤ grade 2 nausea and vomiting. For grade 3 nausea and vomiting refractory to supportive therapy, cisplatin will be held until recovery to < grade 2. No dose reductions will be made.
6. Mucositis: Significant mucositis (grade 3-4, CTCAE, v. 4) is expected from radiation and cisplatin and should not be a reason for a treatment break, unless it significantly interferes with fluid intake or nutrition. Aggressive supportive care is encouraged as well as consideration of a PEG tube if not already done.
7. Ototoxicity: For clinical hearing loss not requiring a hearing aid, reduce cisplatin to 50 mg/m2. For hearing loss requiring a hearing aid, discontinue cisplatin. For grade 2-3 tinnitus (CTCAE, v. 4) at the time of retreatment, hold cisplatin until improvement to grade 1 or less and then reduce the following doses of cisplatin to 50 mg/m2. If tinnitus does not improve to grade 1 or less by the last day of

radiation therapy, discontinue cisplatin. An audiogram is recommended when there is any report of significant change in hearing and/or an increase in tinnitus.

8. Other Toxicities: For any other grade 3-4 adverse events, hold cisplatin until toxicities have recovered to grade 1 or less.
   If the second or third dose of cisplatin is delayed more than 21 days because of hematologic, neurologic, renal, or other adverse events, that dose will be omitted.
   If a weight change of ≥10% occurs, the following cisplatin doses should be adjusted.

5.2.1.4 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 2 days before or after the scheduled Day 1 of each cycle due to administrative reasons. Day 1 cisplatin and radiation can begin up to 7 days earlier (minimum 14 days after pembrolizumab administration) if patient and /or investigator prefer to expedite initiation of radiation.
All trial treatments will be administered on an outpatient basis.
Initiation of subsequent cycles of pembrolizumab therapy may be delayed for up to 6 weeks to allow recovery from all drug-related toxicity. If the subsequent dose of pembrolizumab is delayed more than 6 weeks because of adverse events, pembrolizumab will be discontinued. Initiation of subsequent cycles of cisplatin therapy may be delayed for up to 3 weeks to allow recovery from all drug-related toxicity. If the subsequent dose of cisplatin is delayed more than 21 days because of adverse events, that dose will be omitted. Alternately, the Investigator may choose to administer supportive care (blood product transfusions) for retreatment criteria to be met. If the recovery criteria are not met after a 6-week delay, the patient will be discontinued from study treatment unless, in the opinion of the Investigator, the patient is experiencing a clinical benefit, in which case a decision regarding continuation of treatment will be made on an individual patient basis in consultation with the Merck medical monitor. Justification will be recorded in the source documents.

In the setting of dose delays, neither cisplatin nor pembrolizumab will be administered following completion of radiation therapy.

When initiating a subsequent cycle, a minimum interval of 21 days should be observed between pembrolizumab administrations and between cisplatin administrations.

Cisplatin or pembrolizumab can be given either before or after the radiation therapy fraction that is given on the same day. If radiation is held for more than 2 days (for any reason), cisplatin may be held as well until radiation resumes.
Note: pembrolizumab or cisplatin given within 48 hours of days 1 and 22 and 43 due to holidays, for example, is acceptable). Weekends count as days. Use the actual body weight for all patients. There should be no dose modifications because of obesity.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. 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).

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

5.2.2 Radiation Treatment

5.2.2.1 Dose Specifications

The prescribed radiotherapy dose will be 70 Gy in 2 Gy once-daily fraction size (total of 35 fractions). Radiotherapy should begin on a Monday, Tuesday or Wednesday. The daily dose of 2 Gy will be prescribed such that 95% of the PTV volume receives at least 95% of prescribed dose. The spinal cord dose may not exceed 45 Gy to any volume larger than 0.03 cc.

5.2.2.2 Technical Factors

Treatment Planning/Delivery: Megavoltage energy photon beam irradiation is required. IMRT treatment planning with simultaneous integrated boost (SIB) will be used, and treatment verification films must be taken daily (kv films or cone beam CT).

5.2.2.3 Localization, Simulation, and Immobilization

1. Patients must have an immobilization device (e.g., aquaplast mask extending to shoulders) made prior to treatment planning CT scan.
2. All patients will undergo CT simulation for treatment planning. The treatment planning CT scan may be completed with or without IV contrast. 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 less.

5.2.2.4 Target and Normal Tissue Volume Restrictions

1. *Definition of Target Volumes*

GTV70: This volume includes all gross tumor volume (primary tumor and nodal disease) based on clinical exam, PETCT scan and/or planning CT.

CTV70: This volume will receive 2 Gy per fraction. CTV70 will include the primary tumor plus a 1.0 cm circumferential margin added for microscopic spread. This volume may be decreased in size as appropriate around structures that represent barriers to anatomic spread of tumor, and up to 1.5 cm expansion may be added for suspicion on significant laryngeal movement with swallowing.

CTV56: This will include all other regions felt to be at risk for harboring microscopic cancer that do not meet the criteria for CTV70. For example, this would apply to bilateral necks irradiated electively. This volume will receive 1.6 Gy per fraction.

CTV63 **Optional:** This may be defined at the discretion of the treating radiation oncologist. This would include a region or regions felt to be at especially high risk for recurrence (e.g., first echelon nodal regions that are clinically negative). This area will be receiving a daily fraction size of 1.8 Gy.

Planning Target Volumes (PTVs): In general, the PTV should be pulled 3mm off of skin unless the skin is clinically involved with tumor.
PTV Expansion The CTV-to- PTV expansion is 3 mm as daily image guidance will be employed.
2. *Definition of Normal Tissues/Organs at Risk (OARs)*
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.

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 1⁄2 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 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) excluding the PTVs.

Cervical Esophagus: This will be defined as a tubular structure that starts at the bottom of OARpharynx and extends to the thoracic inlet, excluding the PTVs.
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. It is recognized that for oral cavity cancers, this may overlap with CTVs and PTVs.

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.

5.2.2.5 Treatment Planning and Delivery

1. Dose Prescription to PTVs

As described above, prescribed radiotherapy dose will be 70 Gy in 2 Gy once-daily fraction size. For inverse planning IMRT, the goal is for 95% of the PTV70 to receive 95% of 70 Gy with a minimum dose (cold spot) of no less than 63 Gy.

For IMRT prioritization, PTV70 will be the highest priority target structure. PTV63 and PTV56, if applicable, will be ranked in the IMRT planning as lower priority than PTV70 although higher priority than normal structures other than spinal cord and brain stem.

2. Dose Constraints to Normal Structures

Spinal Cord: The PRVcord should not exceed 45 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). The spinal cord PRV should not exceed 50 Gy to any volume in excess of 0.01 cc. In treatment planning, the spinal cord PRV should be given the highest priority.

Brainstem: The PRVbrainstem 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 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 unless lips involved with primary tumor. The mean dose should be < 20 Gy. The maximum dose will be < 30 Gy.

Oral Cavity: Reduce the dose as much as possible. The suggested mean dose should be < 30 Gy.

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. Additional planning goals may include: 1) At least 50% of one parotid will receive < 30 Gy; and/or 2) At least 20 cc of parotid tissue (from the combination of both glands) will receive < 20 Gy.

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

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. For tumors that were not clinically or pathologically involving the mandible, the CTV should be contoured off the mandible.

5.2.2.6 Compliance Criteria

Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Treatment breaks, if necessary, ideally should not exceed 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.

5.2.2.7 Radiation Therapy Adverse Events

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 will be utilized for grading all adverse events. Placement of a feeding tube should be recorded 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, xerostomia, hoarseness, transient ear discomfort, 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, and skin/soft tissue fibrosis. Much less common radiation adverse events include: mandibular osteoradionecrosis, and cervical myelopathy (< 1% with restriction of spinal cord dose to max dose of 45 Gy).

5.3 Trial Blinding/Masking

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

5.4 Randomization or Treatment Allocation

All patients enrolled in this study will receive the combination of All patients enrolled in this study will receive the combination of pembrolizumab, cisplatin and radiation.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.5.1 Acceptable Concomitant Medications

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

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy to any area other than specified in laryngeal carcinoma treatment protocol
- 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, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. Premedication with steroids may be administered on Cycle 1 Day 1, if required by institutional standards. However, due to their immunosuppressive effect, steroids are encouraged to be discontinued within 72 hours. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

The Exclusion Criteria describes other medications which are prohibited in this trial.
There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.6 Rescue Medications & Supportive Care

5.6.1 Pembrolizumab Supportive Care Guidelines

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 below and in greater detail in the ECI guidance document. 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, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 5.2.1 for dose modification.

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.

- **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. If sufficient oral 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** 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. 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. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - 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.

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.

- 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**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** 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.

- **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 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires 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.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g.,	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	
<u>Grades 3 or 4</u> Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.6.2 Cisplatin Supportive Care Guidelines

- **Fluid and Electrolyte Imbalance**

  Patients must be vigorously hydrated and diuresed before cisplatin administration as per institutional standard regimens.

- **Nausea and Vomiting**

  High dose cisplatin is a highly emetogenic regimen with significant incidence of delayed nausea and vomiting. The following guidelines will be followed:
  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; plus a corticosteroid, such as dexamethasone, up to 20 mg iv.

  Breakthrough nausea and vomiting should be managed at the discretion of the medical oncologist or radiation oncologist.

  Delayed nausea and vomiting (greater than 24 hours after chemotherapy administration) may be managed by the addition of aprepitant concurrently or with metoclopramide and dexamethasone.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to

participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.2-Reporting of Pregnancy and Lactation to the Sponsor and to Merck. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours to the Sponsor and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression
  Note: For unconfirmed radiographic disease progression, please see Section 5.2.2
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements

- The subject is lost to follow-up
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.9 Subject Replacement Strategy

Replacement of Patients in DLT Period

Patients who received <90% of the pembrolizumab infusion in Cycle 1 (e.g., because the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT will not be taken into account in the assessment of the overall DLT rate for the phase I run in cohort and need to be replaced.

If a patient experiences a DLT in Cycle 1, study therapy may be discontinued following discussion and agreement between the Sponsor and Investigator. An alternative consideration may be dose modifications of cisplatin and pembrolizumab as described in Section 5.2.1 with continued therapy.

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

5.10 Clinical Criteria for Early Trial Termination

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

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug

In the event of Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	Screening Phase	Treatment Cycles				End of Treatment		Post-Treatment	Post Progression or new anti-cancer Therapy
Treatment cycle/Title:	Main Study Screening Visit	C1 D-21	C1 D1	C1 D2 2	C1 D43	Discon At time of Discon	Safety Follow-up 30 days post discon	Follow-Up Every 12 weeks(± 1 w)	Survival Follow-Up Phase Every 12 weeks (±1 w)
Scheduling Window (Days):	-28 to -1	-21 to -14	± 2	± 2	± 2				
Informed Consent	x								
Inclusion/Exclusion Criteria	x								
Standard Chemotherapy Administered Cisplatin-100 mg			x	x	x				
Trial Treatment Administration Pembrolizumab 200 mg		x	x₢	x₢	x₢				
Radiation- 70Gy/35 fx			xΔ	x Δ	xΔ				
Survival Status								x	x ∞
Review Adverse Events		x	x	x	x	x	x	x£	

Trial Period:	Screening Phase	Treatment Cycles				End of Treatment		Post-Treatment	Post Progression or new anti-cancer Therapy
						Discon	Safety Follow-up	Follow-Up	Survival Follow-Up Phase
Treatment cycle/Title:	Main Study Screening Visit	C1 D-21	C1 D1	C1 D2 2	C1 D43	At time of Discon	30 days post discon	Every 12 weeks(± 1 w)	Every 12 weeks (±1 w)
Scheduling Window (Days):	-28 to -1	-21 to -14	± 2	± 2	± 2				
Directed Physical Examination		X	X	X	X	X		x¥	
Full Physical Exam	X								
Review of Concomitant Medications	X	X	X	X	X	X	X	X	
Review Medical History	X								
Subsequent Anti-Cancer Therapy Status							X		
Endoscopic Examination in Office	x¢		x¢					x£	
Vital Signs and Weight	x	x	x	x	x	x			
Review Speech/swallow questionnaire ¢	x							x¥	
Review Nutrition questionnaire ¢	x							x¥	

Trial Period:	Screening Phase	Treatment Cycles				End of Treatment		Post-Treatment	Post Progression or new anti-cancer Therapy
						Discon	Safety Follow-up	Follow-Up	Survival Follow-Up Phase
Treatment cycle/Title:	Main Study Screening Visit	C1 D-21	C1 D1	C1 D2 2	C1 D43	At time of Discon	30 days post discon	Every 12 weeks(± 1 w)	Every 12 weeks (±1 w)
Scheduling Window (Days):	-28 to -1	-21 to -14	± 2	± 2	± 2				
ECOG Performance Status	x	x	x	x	x	x			
Functional Oral Intake ¢	X							x¥	
Pregnancy Test – Urine or Serum b-HCG if appropriate	x								
CBC with Differential	x	x	x	x	x				
Comprehensive Serum Chemistry Panel	x	x	x	x	x				
T3, FT4 and TSH	x		x		x				
Tumor Imaging (PET preferred)	x							x£	
Archival or Newly Obtained Tissue Collection	x		x¢						

Trial Period:	Screening Phase	Treatment Cycles				End of Treatment		Post-Treatment	Post Progression or new anti-cancer Therapy
						Discon	Safety Follow-up	Follow-Up	Survival Follow-Up Phase
Treatment cycle/Title:	Main Study Screening Visit	C1 D-21	C1 D1	C1 D2 2	C1 D43	At time of Discon	30 days post discon	Every 12 weeks(± 1 w)	Every 12 weeks (±1 w)
Scheduling Window (Days):	-28 to -1	-21 to -14	± 2	± 2	± 2				
Correlative Studies Blood Collection	x		x					x£	
Urinalysis	x		x		x				

¢ Recommended but not mandatory
£ Only once 12-16 weeks after end of treatment
¥ At 3, 6, 12 months after end of treatment
∆ Continuous daily
Ɋ If patient and clinician need to expedite initiation of chemoradiation, they are allowed to start cisplatin and radiation after a minimum of 14 from first dose pembrolizumab, however, there should be a minimum of 21 days (+/- 2 days) between pembrolizumab doses, thereafter.
∞ patients should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Merck for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.
A copy of the signed and dated consent form should be given to the subject before participation in the trial.

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

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

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

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.1.1.6 Assignment of Screening Number

Patients will be assigned a screening number upon consent.

7.1.1.7 Assignment of Randomization Number

There is no randomization number.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if

clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see the separate ECI guidance document in Appendix 4 regarding the identification, evaluation and management of potential irAEs.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

7.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 11.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

Radiologic assessments of measurable disease will be performed using PETCT imaging. RECIST 1.1 will be used to assess response to therapy. Radiologic imaging will be performed at baseline prior to initiation of treatment and subsequently after completion of s of therapy (14 +/- 2 weeks). Further imaging is not required unless clinically indicated.

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

All patients will be required to submit archival tissue as part of study participation. In patients who do not have archival tissue, a pretreatment tumor biopsy will be performed, unless deemed contraindicated by the treating physician. An attempt to obtain additional tumor biopsies will be performed after 1 dose of treatment if felt safe and feasible. These samples will be submitted centrally for immunohistochemical expression studies involving proteins in the PD-1 family as well as CD3, CD69 and FOXP3. We will also attempt to perform Tumor infiltrating immune cell phenotypes, global gene expression by RNAseq, and whole genome sequencing if adequate tissue available.

Research blood collections will be obtained for correlative research studies on the following time points: Prior to initiation of therapy (day -21 cycle 1), after 1 dose of treatment (day 1 cycle 1), at treatment discontinuation and 14 +/- 2 weeks follow up. We intend to perform flow cytometric evaluation of CD3, CD4, CD8, CD14, PD-1, PD-L1, PD-L2 on peripheral blood mononuclear cells as well as measurement of circulating tumor cells and circulating cell-free DNA.

Specimen Requirements: Submission for flow cytometry

- A 7.5 mL specimen of peripheral blood in a lavender- (EDTA) or green- (sodium heparin) tube is acceptable for each draw.
- Storage/Transport Temperature: Specimens can be transported with a cold pack or wet ice, but do not fix or freeze specimens.
- Unacceptable Conditions: Frozen specimens, specimens greater than 48 hours old, specimens fixed in formalin for flow cytometry
- Address for shipping specimens: Please refer to Standard Operating Procedures for details on blood and tissue shipment:

Josette A. Robinson-Eaton, Sr. Research Assistant

University of Cincinnati Retrovirology Reference Laboratory

231 Albert Sabin Way, Rm. 6159 MSB, Cincinnati, Ohio 45267

Lab: 513-558-4287

Office: 513-558-4790

Fax: 513-558-4711

Email: robinsja@uc.edu

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5.

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin		Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase		(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)		
WBC (total and differential)	Aspartate aminotransferase (AST)		
Red Blood Cell Count	Lactate dehydrogenase (LDH)		Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡		Free tyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
‡ If considered standard of care in your region.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.5. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

7.1.5 Visit Requirements

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

7.1.5.1 Screening

The following assessments will be performed up to 28 days prior to initiation of study treatment:

1. Full Physical Examination
2. Vital Signs and weight
3. Pregnancy test or Serum B-HCG in females of childbearing age (within 72 hours of starting therapy)
4. CBC (within 10 days of starting therapy)
5. Comprehensive Serum Chemistry panel (within 10 days of starting therapy)
6. T3, FT4 and TSH (within 10 days of starting therapy)
7. Imaging within 45 days of starting treatment. PET CT is preferred, but if not considered institution standard, CT head and neck and CT chest with contrast can be substituted.

7.1.5.2 Treatment Period

The following assessments will be performed on day of administration of study treatment and must be performed no more than 24 hours prior to treatment unless otherwise specified. The only exception is for day 1 when the assessments will serve as baseline assessments and can be performed up to 3 weeks prior or as otherwise specified.

1. Adverse event review
3. Directed physical examination

4. Vital signs and weight
5. ECOG performance status
5. CBC
6. Comprehensive serum chemistry panel

7.1.5.3 Post-Treatment Visits

7.1.5.3.1 Safety Follow-Up Visit

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

Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

7.1.5.4 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (12± 1 week) by exam to monitor disease status. Imaging should be performed at 14 weeks (+/-2 weeks) since last treatment (radiation or drug therapy). Further imaging is per decision of treating clinician. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study.

7.1.5.4.1 *Survival Follow-up*

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks (12± 1 week) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.2 Assessing and Recording Adverse Events

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

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events.

Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

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

Adverse events may occur during the course of the use of Merck product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.
Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1.

7.2.1 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 a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product 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 hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

An overdose for cisplatin will be defined as any dose of study drug that is 10% or more over the prescribed dose per cycle as described in the study protocol. There is no specific antidote for cisplatin overdose. In the event of overdose, subsequent dose of cisplatin should be held unless approved by study Sponsor and Merck. Patient should be observed closely for signs of toxicity. As clinically indicated, appropriate supportive treatment should be provided, if applicable.

7.2.2 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)

7.2.3 Immediate Reporting of Adverse Events to the Sponsor and to Merck

7.2.3.1 Serious Adverse Events

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is another important medical event

Refer to Table 6 for additional details regarding each of the above criteria.
Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

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 Merck product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck.

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

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

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

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

1. Additional adverse events:

A separate guidance document has been provided entitled “Event of Clinical Interest Guidance Document” (previously entitled, “Event of Clinical Interest and Immune-Related Adverse Event Guidance Document”). This document can be found in Appendix 4 and provides guidance regarding identification, evaluation and management of ECIs and irAEs.
ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to 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), regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

Table 6 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 Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened 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 test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product 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 Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck product (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? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the 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 the Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability,

		or (2) the trial is a single-dose drug trial); or (3) Merck product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE MERCK PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck product relationship).**
Yes, there is a reasonable possibility of Merck product relationship.		There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.
No, there is not a reasonable possibility Merck product relationship		Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

The primary endpoint is laryngectomy-free survival (LFS) at 18 month. LFS for standard of care is approximately 70%; the trial hypothesis is that LFS at 18 month can be improved to at least 85% using the experimental agent. Forty seven patients are required to identify this improvement in 18 month LFS using a one-sided test with 10% significance and 80% power. This calculation is based on a non-parametric LFS distribution, and assumes that it will take 18 months to accrue all 47 patients, and that an additional 6 months of follow-up will be done after the last patient is enrolled.

Study size was calculated using the SWOG calculator for “one-arm nonparametric survival”: http://www.swogstat.org/statoolsout.html

8.2 Statistical Analysis Plan

Safety run-in phase: Although PD-1 inhibition is not expected to increase the toxicity of chemoradiation therapy, clinical trials of pembrolizumab combined with cisplatin and radiation for locally advanced head and neck carcinoma have not been conducted. In order to protect against unexpected problems a run-in safety analysis will be performed prior to completing the rest of the first stage of study. This safety analysis will occur after 6 analyzable patients are entered into study. Pembrolizumab will be administered initially at the recommended phase II dose of 200 mg q 3 weeks. If more than 2 dose-limiting toxicities (DLTs) in the cohort of 6 patients then pembrolizumab will be given subsequent to completion of chemoradiation. In the event of 0-2 DLT events, the study will proceed as planned. A DLT will be defined as a ≥ grade 3 (CTCAE, v.4) adverse event that is definitely, probably, or possibly related to study drug, excluding grade 3 tumor flare and toxicities that are strongly associated with concurrent radiation and cisplatin (for example rash, mucositis, radiation dermatitis).

LFS will be estimated using the Kaplan-Meier method. The point estimate and standard error will be obtained from the Kaplan-Meier curve and a 95% confidence interval will be calculated to estimate 18-month LFS. A z-test will be used to test the primary hypothesis of improvement in 18- month LFS from 70% to 85%.

One-year LFS, Progression-free survival, overall survival, event-free survival, and patterns of failure will be estimated using the Kaplan-Meier method. Complete response at 3 months will be estimated with an exact 95% confidence interval.
For correlative studies, prognostic factors for complete response will be identified using logistic regression analysis. Prognostic factors for outcomes will be identified using Cox proportional hazards analysis.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by Merck as summarized in Table 7.

Table 7 Product Descriptions

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

9.2 Packaging and Labeling Information

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

9.3 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.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.
Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

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

9.5 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.

9.6 Cisplatin

Refer to the package insert for detailed pharmacologic and safety information

1. **Formulation:**

Each ml contains 1 mg cisplatin and 9 mg of sodium chloride in water for injection. Hydrochloric acid and/or sodium hydroxide is added for adjustment. Vials are multi-dose, available as an aqueous solution, with a final concentration of 1 mg/1 mL cisplatin. The pH range of aqueous product is 3.8 to 5.9. Vials should be stored at 20-25ºC (68-77 ºF), and protected from light.

2. **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.

3. **Administration:**

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

4. **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.

5. **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.

6. **Supply:**

Cisplatin is commercially available. The use of drug(s) or combination of drugs in this protocol meet the criteria for IND exemption.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

Patient records will be kept in a secure location at the University of Cincinnati accessible only to research authorized personnel. The patient identity will be kept as confidential as possible as required by law. Except as required by law, the patient will not be identified by name, social security number, address, telephone number, or any

other direct personal identifier. Study subjects will be assigned an ID code. Information about the code will be kept in a secure location and access limited to research study personnel. The results of this research study may be presented at scientific or medical meetings or published in scientific journals. However, the patient identity will not be disclosed. The patient's personal data which may be included in the investigator's database shall be treated in compliance with all applicable laws and regulations.

10.2 Compliance with Financial Disclosure Requirements

Compliance standards established by University of Cincinnati will be followed.

10.3 Compliance with Law, Audit and Debarment

Compliance standards established by University of Cincinnati will be followed.

10.4 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.

10.5 Quality Management System

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Cancer Consortium IRB and Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation.

The University of Cincinnati Consortium Data and Safety Monitoring Board (DSMB) will be the monitoring entity for this study in accordance with the Cancer Consortium's Data Safety Monitoring Plan.

10.6 Data Management

The Protocol Director, or her designees, will prepare and maintain adequate and accurate participant case histories with observations and other data pertinent to the study. Original source documents should be transcribed to Case Report Forms (CRFs) and used to analyze the study data. Source documents include hospital records, clinical charts, laboratory and pharmacy records, and recorded electronic data.

All data required by the trial will be entered onto paper and electronic case report forms. Any corrections to data required into the paper case report forms must be made in such a way that the original entry is not obscured. Only designated study staff will

enter data for study participants after study visits. Case report forms will be checked against source document data by study staff.

Trial oversight will be carried out by the Protocol Director, Dr. Nooshin Hashemi Sadraei, and her research staff. They will meet weekly to review recently acquired data and adverse events. The data recorded within the research charts and protocol database is compared with the actual data that is available from the medical record and/or clinical histories. Data detailed in the research case report forms includes the nature and severity of all toxicities, which are also reported as described above. All investigators on the protocol will receive formal training in the ethical conduct of human research. Institutional support of trial auditing is provided in accordance with the Cancer Consortium's Data and Safety Monitoring Plan. In addition, protocols are reviewed at least annually by the Scientific Review Committee (SRC) and the Institutional Review Board (IRB).

11.0 APPENDICES

11.1 ECOG Performance Status

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

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

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

11.3 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

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

* As published in the European Journal of Cancer:
E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R.

Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

In addition, volumetric analysis will be explored by central review for response assessment.

11.4 Events of Clinical Interest Guidance Document

Please refer to section 5.6.1

11.5 References

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