SPONSOR: Trisha Wise-Draper M.D., Ph.D., University of Cincinnati

TITLE: Phase II Investigation of Adjuvant Combined Cisplatin and Radiation with Pembrolizumab in Resected HNSCC

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Protocol #: UCCI-HN-15-01

Title: Phase II Investigation of Adjuvant Combined Cisplatin and Radiation with Pembrolizumab in Resected HNSCC.

Coordinating Center: University of Cincinnati Cancer Center

Principal Investigator & Medical Oncologist Chair:
Trisha Wise-Draper, MD, PhD
3125 Eden Ave
Cincinnati, OH 45267-0562
Telephone: 513-558-2826
Fax: 513-558-6703
wiseth@ucmail.uc.edu

Head and Neck Surgeon Chair
Keith Casper MD, (UMich)

Medical Oncologist Co-Chair
Maura Gillison, MD, PhD (MDA)

Radiation Oncology Chair
Michelle Mierzwa, MD (UMich)

Collaborating Centers: The Ohio State University (OSU), Medical University of South Carolina (MUSC), University of Louisville (UofL), University of Michigan (UMich), MD Anderson (MDA)

Principal Investigator (OSU): Matthew Old, MD
Principal Investigator (MUSC): Paul O'Brien, MD
Principal Investigator (MD Anderson): Maura Gillison, MD, PhD
Principal Investigator (UofL): Neal Dunlap, MD
Principal Investigator (UMich): Frank Worden, MD

Laboratory Studies: Laura Conforti, PhD
University of Cincinnati

Edith Janssen, PhD
CCHMC

Statistician:
J. Jack Lee
MD Anderson
Roman Jandarov
University of Cincinnati

Pathologist:
Ben Hinrichs
University of Cincinnati

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1.0 TRIAL SUMMARY

Abbreviated Title	Adjuvant HNC anti-PD1 chemoradiation phase II study
Trial Phase	Phase II
Clinical Indication	High and Intermediate risk resected HNC
Trial Type	2 arm, non-randomized
Type of control	Historical
Route of administration	IV
Trial Blinding	None

Treatment Groups	High risk and Intermediate risk
Number of trial subjects	80
Estimated enrollment period	3 years
Estimated duration of trial	8 years (5 years disease free survival (DFS) + 3-year enrollment period)
Duration of Participation for subjects	5 years

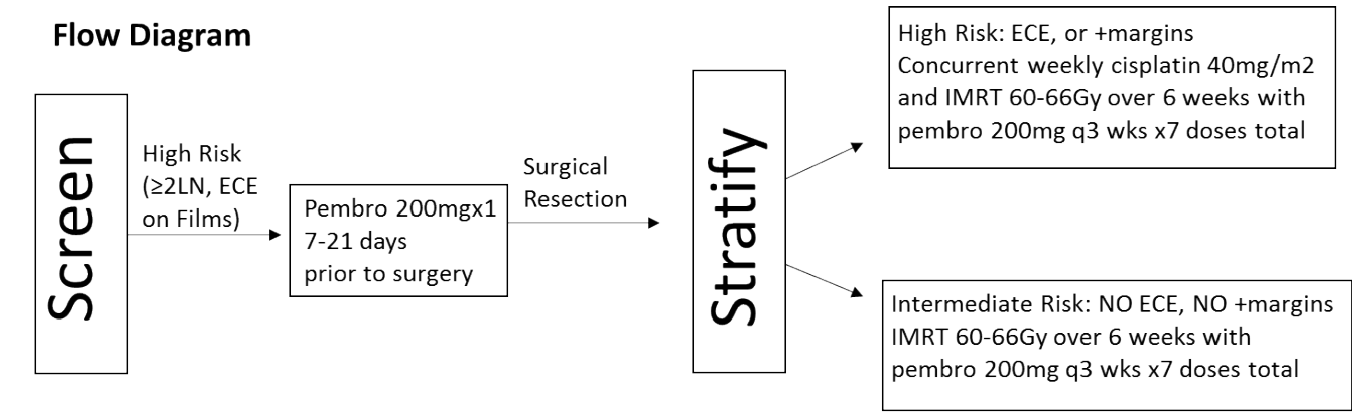
2.0 TRIAL DESIGN

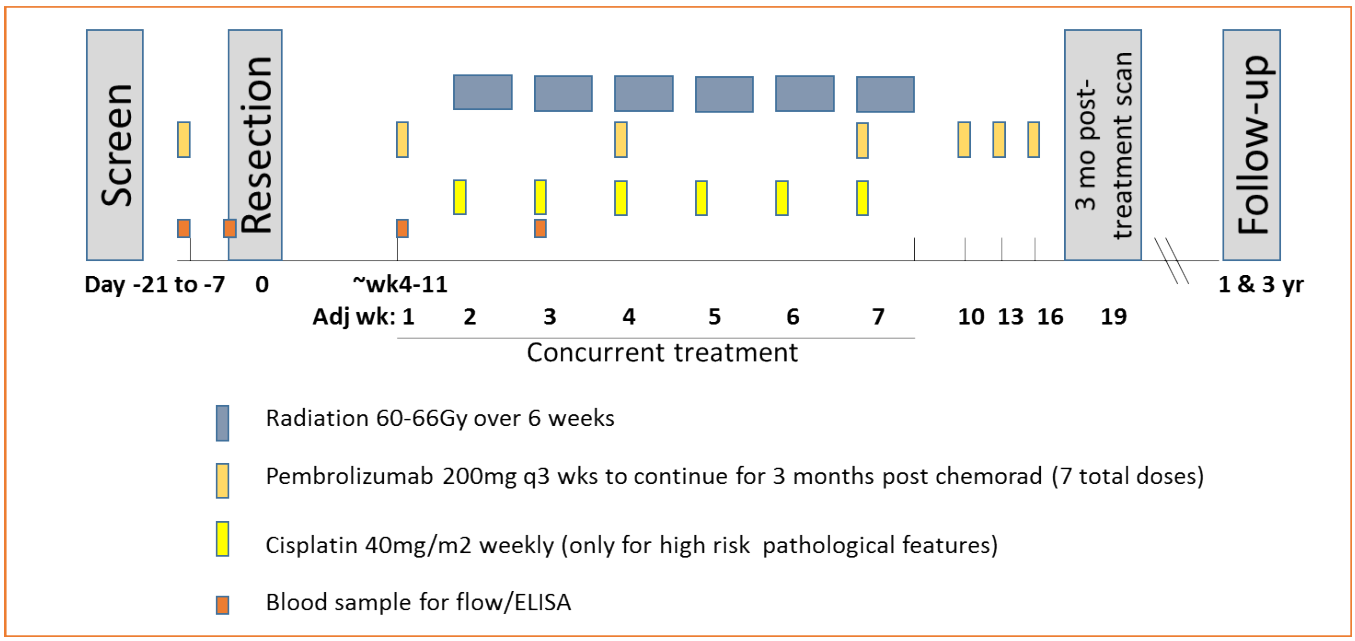
2.1 Trial Design

This study will be a two arm phase II trial including 80 patients with head and neck squamous cell carcinoma (HNSCC) eligible for resection. Patients who are identified to be clinically high risk (see inclusion) prior to resection will be screened and consented to receive 1 dose Pembrolizumab followed by resection. Post-resection, patients will be stratified and if high risk features are confirmed by pathology (extracapsular extension [ECE], or positive margins), patients will receive concurrent weekly Cisplatin, daily radiation and every three week Pembrolizumab as shown in schema. If those enrolled prior to resection are found to not have high risk pathological features, they will go on to receive radiation and Pembrolizumab. Eight patients from each group will be enrolled as part of a lead-in on a rolling basis to determine the safety of this combination with stopping rules if expected toxicity is exceeded. There will be a fair proportion of patients who are identified to be high risk prior to resection but do not have confirmed high risk pathologic features. Therefore, we expect that using our criteria, that at least 50% (or 40 patients) will have high risk features requiring chemotherapy in addition to radiation (CRT) and Pembrolizumab while the remaining intermediate risk patients will receive radiation and Pembrolizumab. For correlative studies, archived or fresh biopsy samples and resection tissue will be assessed by H&E and IHC for immune phenotype. Blood samples will also be collected as described in section 7 for correlative studies. Patients will be followed approximately weekly during treatment, then monthly for the first 3 months following treatment and then every 3 months thereafter for the first two years. A repeat PET/CT or CT scan will be performed at 3 months post-treatment to assess for early relapse. Patients will be assessed every 3 months for the first 2 years and then every 6 months for the next 3 years for disease free survival (DFS) and overall survival (OS).

2.2 Trial Diagram

Flow Diagram





3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objectives & Hypotheses

(1) **Objective:** Determine the frequency and severity of side effects of Pembrolizumab when administered in combination with radiation alone or Cisplatin and radiation therapy (CRT) in patients undergoing adjuvant treatment for resected HNSCC.

- **Hypothesis:** Combining Pembrolizumab with concurrent Cisplatin and radiation will be safe, causing minimal interruption to standard of care therapy in patients with resected HNSCC.

(2) **Objective:** To estimate the 1 and 3 year disease free survival (DFS) combining Pembrolizumab with adjuvant CRT in patients with resected high risk HNSCC.

- **Hypothesis:** Combining Pembrolizumab to concurrent Cisplatin and radiation will increase DFS in patients with resected HNSCC relative to historic data as there is not a current comparison in this trial.

(3) **Objective:** To estimate the 1 and 3 year disease free survival (DFS) combining Pembrolizumab with adjuvant radiation in patients with resected intermediate risk HNSCC.

- **Hypothesis:** Combining Pembrolizumab to radiation will increase DFS in patients with resected HNSCC relative to historic data as there is not a current comparison in this trial.

3.2 Secondary Objectives & Hypotheses

(1) **Objective:** To estimate the 1 and 3 year overall survival (OS) combining Pembrolizumab with adjuvant CRT in patients with resected high risk HNSCC.

- **Hypothesis:** Combining Pembrolizumab to concurrent Cisplatin and radiation will increase OS in patients with resected HNSCC relative to historic data as there is not a current comparison in this trial.

(2) **Objective:** To estimate the 1 and 3 year overall survival (OS) combining Pembrolizumab with adjuvant radiation in patients with resected intermediate risk HNSCC.

- **Hypothesis:** Combining Pembrolizumab to radiation will increase OS in patients with resected HNSCC relative to historic data as there is not a current comparison in this trial.

(3) **Objective**: Determine the change in distribution of the tumor immune microenvironment before and after Pembrolizumab administration in tumor biopsy tissue using markers of T cells and T cell activation including but not limited to CD4, CD8, CD38, HLA-DR, PD-1 and PD-L1.

- **Hypothesis**: Pembrolizumab administration will result in enhanced immune stimulation in tumors marked by T cell infiltration/activation.

(4) **Objective**: Determine the baseline adenosine receptor expression in HNSCC patients and the effect of PD-1 inhibition by Pembrolizumab in activated T cells combined with peripheral T cell activation by flow cytometry.

- **Hypothesis**: Pembrolizumab administration will result in increased adenosine receptor expression which will confer resistance to T cell activation.

3.3 Exploratory Objectives

(1) Objective: Determine immunoregulatory activity in the serum including immune related cytokines including but not limited to IL-2 and IL-6.

(2) Objective: Study peripheral blood T cell and tumor infiltrating lymphocyte functionality (motility, calcium response to antigen presentation, ion channel function, cytotoxicity, apoptosis and cytokine release) to see if and what type of functionality is gained after anti-PD1 treatment.

(3) Objective: Assess the presence of myeloid derived suppressor cells, pro- and anti-inflammatory monocytes and dendritic cells in the blood and tissue at the different points of treatment as a

marker of prognosis using staining that would include, but not be limited to CD14, CD16, CD11c, CD1c, CD303, CD141, CD68, PDL-1, CD33, GR1, and HLA-DR.

(4) Objective: Assess disease free and overall survival at 5 years.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

4.1.1 Pharmaceutical and Therapeutic Background

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, PD1 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). It is now known that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and two different PD-1 inhibitors, Pembrolizumab and nivolumab, are FDA approved for therapeutic intervention in melanoma (as well as squamous cell carcinoma of the lung for nivolumab).

Pembrolizumab specifically 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 States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

4.1.2 Preclinical and Clinical Trial Data

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

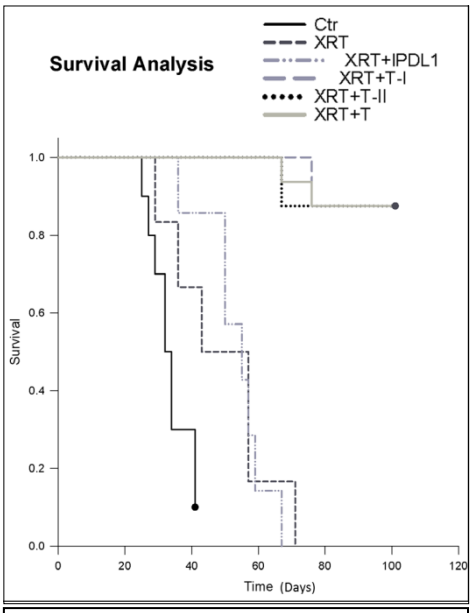
4.1.3 Adjuvant treatment in Head and Neck Cancer

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide. Although early stage tumors are often cured with surgery or radiation, up to 60% of patients present with locally advanced disease requiring multimodality treatment. Many patients with locally advanced disease will undergo upfront surgical resection, but unfortunately, the rate of relapse both locally and distantly after surgery alone is high, particularly in patients with high risk features (multiple lymph node involvement, extracapsular spread or those with positive surgical margins). Two pivotal studies by the EORTC and RTOG published in 2004 demonstrated increased progression free[1,2] and overall survival[1] in patients who received adjuvant concurrent Cisplatin and radiation albeit with higher toxicity over radiation alone. However, PFS and OS were only 47% and 53% respectively at 5 years and even lower if HPV positive patients were excluded. Follow-up meta-analysis by Bernier et al. in 2005 demonstrated that the only common characteristics between both studies who received benefit from the addition of chemotherapy to radiation were ECE and positive margins[3]. Approximately 70% of the patients in the EORTC and 59% of RTOG study had one or both of these high risk features which may explain why overall survival benefit was seen in the EORTC trial only. When the data was pooled together from both studies, the risk of relapse in the high risk group was reduced by 42% whereas those without these features did not seem to benefit from the addition of chemotherapy. Currently standard of care per NCCN guidelines consists of chemotherapy and radiation for this high risk group and radiation only in those with intermediate features (multiple lymph node involvement, perineural invasion, etc). However, despite current standards, patients continue to have high rates of relapse in both groups. In fact, even patients (combined risk factors) who received CRT in the EORTC study had a DFS of only 48% at 5 years (54% at 2 years in the RTOG study) suggesting that novel treatments are necessary in order to improve outcomes in these patients.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Interestingly, the negative immune cell regulator, PD1 ligand-1 (PD-L1), has been found to be up-regulated on many tumors as mentioned above including HNSCC. Recently, Pembrolizumab was shown to have activity in metastatic HNSCC with a decrease in tumor burden in up to 46% of patients with recurrent and metastatic HNSCC (ASCO 2014) leading to the initiation of a phase III study in this group. Besides PD-L1 expression, it was shown that patients with low tumor burden had increased response rates to Pembrolizumab. Therefore, patients who have had the bulk of their disease resected may have a superior response. Additionally, Dr. John Morris' laboratory and others have demonstrated that MHC-1, PD-L1, and preliminarily PD-L2 are further increased in response to radiation treatment suggesting a possible mechanism of resistance and that anti-PD-1 rather than anti-PD-L1 would result in less resistance. Importantly, 1 week pre-treatment with anti-PD-L1 antibody prior to radiation (but not 5 days post-radiation treatment) resulted in increased survival of mice bearing HNSCC tumors (see figure 2) compared to radiation alone. Additionally, others have demonstrated that PD-L1 is also increased in response to Cisplatin exposure. Therefore, we hypothesize that *the addition of Pembrolizumab prior and concurrently to combined radiation or Cisplatin and radiation (CRT) after surgical resection in high risk HNSCC will result in enhanced tumor response*.



PD-L1 expression is upregulated in response to irradiation *in vitro* and *in vivo*

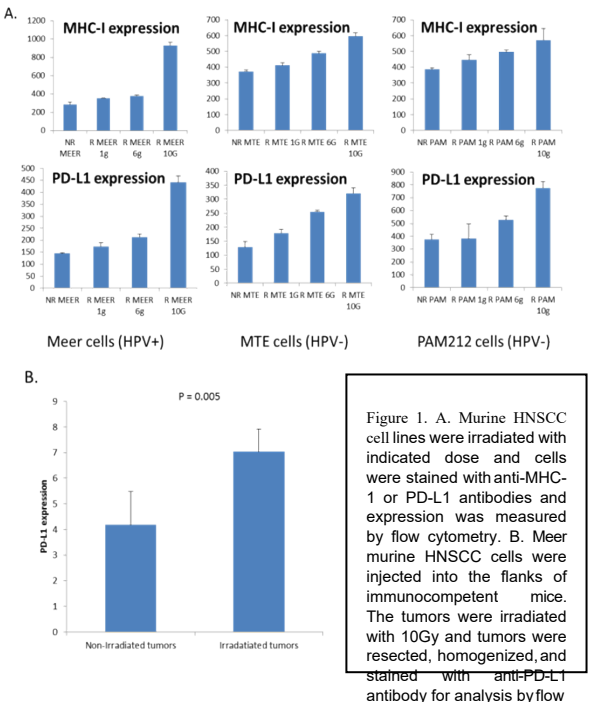


Figure 1. A. Murine HNSCC cell lines were irradiated with indicated dose and cells were stained with anti-MHC-1 or PD-L1 antibodies and expression was measured by flow cytometry. B. Meer murine HNSCC cells were injected into the flanks of immunocompetent mice. The tumors were irradiated with 10Gy and tumors were resected, homogenized, and stained with anti-PD-L1 antibody for analysis by flow

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Pembrolizumab

An open-label Phase I trial (Protocol 001) was conducted to evaluate the safety and clinical activity of single agent 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 was identified.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life. Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provided scientific rationale for testing a Q2W and Q3W dosing schedule.

Similar efficacy and safety of Pembrolizumab was seen when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients. In addition, there was a flat exposure-response relationship of Pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W which did not depend on tumor burden.

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.

4.2.2.2 Cisplatin

Cisplatin is often given as either bolus dosing or weekly dosing when combined with radiation treatment in HNSCC. In locally advanced disease without surgical resection, patients are often offered bolus Cisplatin dosing at 100mg/m2 days 1, 22 and 43 of radiation based off a pivotal study by Adelstein et al.[4] The same dosing was used in the older adjuvant studies mentioned above but with a significant increase in toxicity over radiation alone especially in regards to increase in renal dysfunction, myelosuppression, ototoxicity and emetogenesis. In the post-operative setting, in which many patients have poor nutrition and decreased functional status, there is a concern that patients would not be able to tolerate this bolus dosing and other dosing schedules would be more ideal. Based on data from Ang et al. 2004, it was proposed that patients require at least a cumulative dose of 200mg/m2 of Cisplatin regardless of the dosing schedule (fractionated, high dose, weekly)[5]. Weekly Cisplatin was also shown to be effective with concurrent radiation in nasopharyngeal cancer and was demonstrated to result in lower toxicity over the standard dosing, further strengthening a role for this dosing schedule in HNSCC[6]. NRG has established weekly dosing to be the current standard for adjuvant studies and is currently being used in RTOG 1216 and 0920. Therefore, we feel weekly dosing (40mg/m2 for 6 doses) is most appropriate in this patient population.

4.2.3 Rationale for Endpoints

4.2.3.1 Safety Endpoints

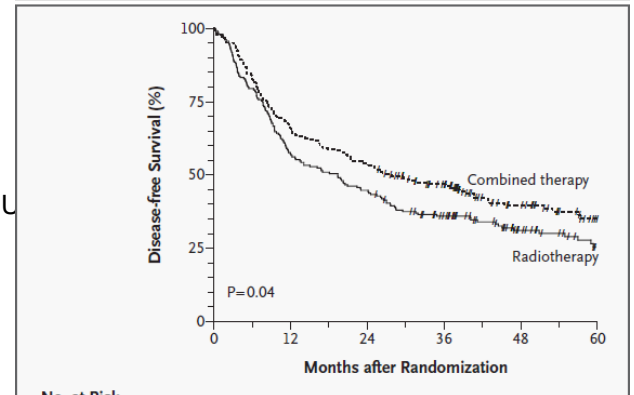
Clinically, the addition of Pembrolizumab to Cisplatin and radiation has yet to be explored. Pre-clinically, the addition did not add any unexpected toxicity in small analyses. Based on the current safety profile of Pembrolizumab alone, and the fact that the toxicities are unique to immunotherapy compared to radiation and chemotherapy, we do not expect to observe any additional adverse effects and that this will therefore be a safe combination. However, because this combination has not yet been explored in this setting (although many clinical trials are currently being designed), we will continue to monitor safety throughout this study using CTCAE guidelines. We will perform a lead-in of 8 patients in each arm in order to determine any unexpected toxicities beyond what had been documented for these therapies. As long as current standard of therapy is not felt to be significantly impacted (delay in >2 out of 8 patients in each arm), the trial will proceed.

4.2.3.2 Efficacy Endpoints

This is a phase II non-randomized study and therefore will rely on historical controls for the primary efficacy endpoint of disease free survival (DFS) in resected high risk HNSCC. Based on the pivotal RTOG 9501 and EORTC 22931 adjuvant studies, disease free survival at 1 year was approximately 66% and 76% respectively for the CRT arms and 58% and 72% respectively for radiation only arms (See table). The 3 year estimates are somewhat closer between the two studies.

Study Group	RTOG 9501		EORTC 22931	
	RT	CRT	RT	CRT
Disease Free Survival 1 year	58%	66%	72%	76%
Disease Free Survival 3 year	37%	47%	40%	57%

There were several differences in these studies including number of lymph nodes involved (94% had ≥ 2 lymph nodes in RTOG versus only 57% in EORTC) and the number of patients with at least 1 high risk feature (ECE or positive margins) was also different (approximately 70% of the patients in the EORTC and 59% of RTOG



study) which may account for these differences.

Based on phase I data, Pembrolizumab resulted in response rates up to 46% at least in those patients positive for PD-L1. Therefore, we expect that the addition of Pembrolizumab will significantly reduce the chance of relapse in this population and therefore, will result in improved DFS. Most locoregional relapses (the most common cause of death in this group) occur within the first year. Therefore, our primary and secondary endpoints respectively will be DFS at 1 and 3 years, which will reflect early and late relapse. Our historical baseline will be based off the RTOG 9501 data due to the fact that entry criteria included either ECE, positive margins or ≥2 lymph nodes all of which are considered to be either high risk or high-intermediate risk which is the group we are most interested in for this study and encompasses our inclusion criteria.

4.2.3.3 Biomarker Research

It has been established that the expression of PD-L1 on tumors and PD-1 on T cells in the microenvironment, confers a poor prognosis in HNSCC. In addition, the frequency of peripheral blood myeloid derived suppressor cells also strongly correlates with a poor prognosis. However, the inhibition of the PD-1/PD-L1 interaction results in impressive tumor responses in a variety of tumors. It is assumed that this is mediated through T-cell mediated tumor cell killing. However, the contribution of the microenvironment remains unclear. Additionally, analysis of tissue after inhibition of this response and the effect on the tumor microenvironment remains relatively unexplored. In this study, we have the unique opportunity to analyze resected tumor tissue after exposure to 1 dose of Pembrolizumab which will give insight to these processes. In addition, the mechanism of resistance to PD-1/PD-L1 inhibition is unclear. As mentioned in the background, up-regulation of PD-L2 may be an explanation for poor responses to PD-L1 inhibition but would not explain the lack of effect in at least 50% of patients to anti-PD-1. Here we will investigate possible novel mechanisms of resistance described in detail below.

<u>Tumor Microenvironment and Mechanism of Resistance to anti-PD-1</u>

The tumor microenvironment exerts an immune suppressive role in cancer by limiting the capacity of T cells to accumulate among cancer cells resulting in immune-mediated cell death[7]. Various aspects of the tumor microenvironment have been shown to limit T cell function: hypoxia, indoleamine 2,3-dioxygenase (IDO), adenosine and PGE2[7]. The suppressive effects of adenosine and hypoxia on T lymphocytes are mediated by ion channels (Kv1.3 and KCa3.1)[8-12]. Both adenosine and PGE2 signal through their respective receptors, cAMP/PKA and their effect in mast cells is mediated by KCa3.1 channels[12-15]. Evidence exists that alterations of the tumor microenvironment improve the efficacy of

immune checkpoint blockade. In a recent study in mice, the combination therapy of anti-PD1 with blockers of the adenosine receptor ($A_{2A}R$) proved to be superior to anti-PD1 monotherapy[16]. On the other hand, the anti-PD1 therapy could also make the immune cells more sensitive to the tumor microenvironment as it has been reported that PD1 blockade in mice increases the expression of $A_{2A}R$ in tumor infiltrating T lymphocytes (TILs). The goal of this collateral study is to determine whether (1) the tumor microenvironment and tumor microenvironment-related features of TILs at baseline (pre-drug) can be used as predictors of responders and non-responders; (2) anti-PD-1 treatment alters the characteristics of TILs making them more susceptible to the immune suppression of the tumor microenvironment with the consequent development of resistance to anti-PD-1 therapy; (3) unique alterations of T cell phenotype and function pre-drug or after therapy can be found in peripheral blood T cells.

5.0 METHODOLOGY

5.1 Eligibility Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Histologically or cytologically confirmed locally advanced HNSCC including the oral cavity, larynx or pharynx (except nasopharynx).

5.1.2 Subject Inclusion Criteria

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

1. Be willing and able to provide written informed consent for the trial.

2. Be ≥ 18 years of age on day of signing informed consent.

3. Patients who are eligible for resection must have one or more of the following clinical features:
    a. Any T stage with ≥ N2 disease;
    b. T4 disease, any N stage;
    c. T3 Oral Cavity, any N stage; or
    d. Clinical evidence of extra-capsular extension on scans.

4. Pre-operative scans including chest imaging preferably PET/CT and CT neck w/contrast. (CT chest and CT neck w/contrast would also be acceptable). If contrast is contraindicated, MRI neck is acceptable.
5. Must be willing to undergo definitive resection with neck dissection.

6. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion before study drug administration if unable to provide archived biopsy tissue. Please note sample does not have to be sent to UC prior to enrollment in study as long as it is documented that

sample exists prior to treatment. (For MDA only, patients with available archival tissue will also have a mandatory fresh biopsy at enrollment.)

7. Have a performance status of 0 or 1 on the ECOG Performance Scale.

8. 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 the screening exam)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	within upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 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
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.	

9. Female subjects 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.

10. 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.
11. 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. 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. Short bursts of steroids of 5-7 days (for COPD exacerbation or other similar indication) are allowed.

2. Has nasopharyngeal or sinonasal carcinoma.

3. Has confirmed metastatic disease. Metastatic disease to neck nodes is considered locally advanced disease and not metastatic and therefore is allowable.

4. Patients who have HPV+ disease of oropharynx. HPV+ disease outside of oropharynx is acceptable.

5. Has a known history of active TB (Bacillus Tuberculosis).

6. Hypersensitivity to Pembrolizumab or any of its excipients.

7. Has a known additional malignancy that was diagnosed within the last five years that is either 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.

8. 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 (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

9. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

10. Has an active infection requiring systemic therapy.
11. 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.

12. Has known psychiatric or substance abuse disorders that, in the opinion of the investigator, would interfere with cooperation with the requirements of the trial.
13. 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.
14. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
15. Has known Hepatitis B (e.g., HBsAg reactive) or known Hepatitis C (e.g., HCV RNA [qualitative] is detected).
16. 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 Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab (Initial infusion)	200 mg	once	IV infusion	Day -21 to -7 (prior to resection)	Experimental
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle starting 7 days before CRT for 7 doses (including initial dose)	Experimental
Cisplatin	40mg/m2	Weekly	IV infusion	4-8 weeks after resection for 6 doses to begin with radiation	Standard of Care for High Risk only

Radiation	60 Gy	Daily M-F	IMRT	4-8 weeks after resection over 6 weeks	Standard of care

Treatment will be administered on an outpatient basis. Protocol treatment (pre-surgical Pembro dose) must begin only after eligibility criteria are confirmed by the UC PI (registration), see study flow for more specific timeframes.

5.2.1 Pretreatment Evaluations/Management

Note: This section lists baseline evaluations needed before the initiation of protocol treatment that **do not** affect eligibility.

5.2.1.1 Required Evaluations/Management

1. Standard of care dental evaluation with management within 3 months prior to the start of radiation.

2. Assessment of swallowing function/dysphagia using CTCAE, v. 4 criteria prior to the start of radiation.

5.2.1.2 Highly Recommended Evaluations/Management

1. Assessment by dietician with recommendations on diet during and after treatment as well as evaluation for prophylactic gastrostomy tube placement (especially if the patient is ≥ 10% below ideal body weight) within 4 weeks prior to the start of adjuvant treatment.

2. Audiogram evaluation as needed.

3. EKG within 8 weeks prior to the start of treatment.

5.2.2 Dose Selection/Modification

5.2.2.1 Dose Selection

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

5.2.2.2 Dose Administration

5.2.2.2.1 Cisplatin Guidelines

Cisplatin 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. Cisplatin should only continue during radiation and doses should not be made up after the completion of radiation. Patients should receive no more than 6 total doses.

(Note: Cisplatin given within 24 hours of planned administration due to holidays, for example, is acceptable). Weekends count as days.
Patients must be vigorously hydrated before and after Cisplatin administration as per institutional standard regimens. Adequate diuresis is recommended per clinical discretion. A suggested, but not mandatory regimen, would be pre- hydration with 1 liter ½ NS with 1 g MgSO4 and KCL 20mEq over 2 hours and to repeat same after Cisplatin (pre-and post-hydration). Other suggested, but not mandatory, regimens could be 1-1.5 liter NS pre-hydration followed by addition 1-1.5 liter NS post-hydration. Any pre-existing dehydration should be corrected, and additional days of IV fluid can be considered per clinical discretion.

5.2.2.2.2 Pembrolizumab Guidelines

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Infuse pembrolizumab (MK-3475) over approximately 30 minutes, with a window of -5 and +10 minutes, through a peripheral line or indwelling catheter. The first dose will be given no more than 3 weeks and no less than 7 days prior to resection. Ideally, the pre-surgery dose of Pembrolizumab will be given between 1-2 weeks before surgery. Post-surgery, Pembrolizumab will be between 4 and 11 weeks and will continue during radiation and 3 months after completion. The first adjuvant Pembrolizumab dose is to begin 1 week prior to radiation.

Pembrolizumab will be administered before Cisplatin on days they are given together. If fluids are administered along with Pembrolizumab, then hydration should include only NS. Radiation may be given before or after infusions. If a Pembrolizumab dose is missed outside the +/-1 day window up to week 7 and +/-3 day window week 10 and beyond per the schedule of events, it should be skipped and not made up.

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

5.2.2.2.3 Radiation Therapy Guidelines

5.2.2.2.3.1 Dose Specifications:
The prescribed radiotherapy dose will be 60-66 Gy in 2-2.2 Gy once-daily fraction size (total of 30-33 fractions). Radiotherapy should begin on a Monday, or Tuesday. The daily dose of 2-2.2Gy 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.

5.2.2.2.3.2 Technical Factors
Treatment Planning/Delivery: Megavoltage energy photon beam irradiation is required. 3D conformal

or IMRT treatment planning may be may be used, and daily IGRT will be used.

5.2.2.2.2.3 Localization, Simulation, and Immobilization

1. Patients must have an immobilization device (e.g., aquaplast mask) 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.

5.2.2.2.2.4 Target and Normal Tissue Volume Restrictions

Definition of Target Volumes

CTV60: CTV60 will include the primary tumor bed (based on preoperative imaging, preoperative physical exam/endoscopy, operative findings, pathologic findings) plus the post-operative neck. This volume may include the skin. It is recognized that after surgery, there can be considerable distortion of normal anatomy. If possible, preoperative GTV(s) should be fused onto the postoperative radiation therapy planning CT scan, and appropriate margins added for microscopic spread (1.5-2 cm). CTV60 also will include the ipsilateral pathologically positive hemineck (if both sides of the neck are proven pathologically positive, CTV60 will include both sides). This generally means encompassing nodal levels 2a, 3, and 4. Nodal levels 1, 2b, 5a, and 5b are included in CTV60 in selected circumstances. For questions, contact the Lead Radiology/Oncology Investigator, Dr. Michelle Mierzwa.

CTV56: This will include all other regions felt to be at risk for harboring microscopic cancer that do not meet the criteria for CTV60. For example, this would apply to the contralateral hemineck being irradiated electively for a midline primary cancer.

CTV66 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., an area of very close margin of resection or nodal extracapsular extension).

Planning Target Volumes (PTVs): In general, the PTV should not go outside of the skin surface; if it does exceed the skin surface, the application of bolus material over this portion of the PTV may be considered to treat skin to full dose.

PTV Expansion The minimum CTV-to- PTV expansion is 3 mm (a larger expansion may be necessary for a target volume subject to significant intra-fraction variability, such as the non-immobilized oral tongue). In general, the CTV-to-PTV expansion should not exceed 10 mm.
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 “uninvolved” posterior pharyngeal wall plus adjacent constrictor muscles. This extends from the superior constrictor region (the inferior pterygoid plates level) to the cricopharyngeal inlet (posterior cricoid cartilage level). This should not overlap 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.

Glottic/Supraglottic Larynx (GSL): Obviously, for patients who have had a total laryngectomy, this structure is not applicable. 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.

5.2.2.2.2.5 Treatment Planning and Delivery Dose Prescription to PTVs

As described in Section 5.2.2.2.2.1, prescribed radiotherapy dose will be 60-66 Gy in 2-2.2 Gy once daily fraction size. For inverse planning IMRT, the goal is for 95% of the PTV60 to receive 95% of 2 Gy with a minimum dose (cold spot) of no less than 56 Gy. It is recognized that portions of the PTV60 close to/within the skin may receive significantly less than 56 Gy. Bolus should be considered for these cutaneous areas deemed to be at risk for microscopic disease.

For IMRT prioritization, PTV60 will be the highest priority target structure. PTV66 and PTV56, if applicable, will be ranked in the IMRT planning as lower priority than PTV60 although higher priority than normal structures other than spinal cord and brain stem.

5.2.2.2.2.6 Dose Constraints to Normal Structures

Spinal Cord: The PRVcord (as defined in Section 6.4.2.1) 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 (as defined in Section 6.4.2.2) 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 < 35 Gy.

Oral Cavity: (uninvolved) Reduce the dose as much as possible. The 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. 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. For oral or oropharyngeal cancer, some recommended (but not mandatory) treatment goals include: 1) No more than 33% of the esophagus exceeds 45 Gy; 2) Mean dose < 35 Gy; 3) No more than 15% of the esophagus exceeds 54 Gy. For larynx cancer, higher doses are expected and permitted. 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.

Glottic and Supraglottic larynx (GSL): Reduce the dose as much as possible. Goal should be mean < 35Gy.

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.
Unspecified Tissue Outside the Targets: For the typical case in which there is no CTV66, no more than 5% of unspecified tissue can receive greater than 58 Gy and no more than 1% or 1cc of unspecified tissue can receive 64 Gy or more. When a boost is used to increase the dose to high risk regions to as much as 66 Gy, these numbers can be increased. In this case, no more than 5% of the unspecified dose should exceed the level of the boost dose, and no more than 1% or 1 cc should exceed the boost dose value plus 10%.

5.2.2.2.2.7 Compliance Criteria

Treatment breaks for radiation 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.

5.2.2.2.2.8 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 adverse event "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).

5.2.2.3 Lead-in Population for Safety Analysis

The first eight patients from each arm will be enrolled as the lead-in population. Safety analysis will be performed with this population and will be analyzed on a rolling basis. Weekly conference calls with all the sites will be held to determine if any of these first 8 patients have experienced a dose limiting toxicity, DLT, (described below) to evaluate the safety of the combination as well as the safety of administering Pembrolizumab before surgery. Safety analysis will be considered complete for each arm at four weeks after the eighth patient has finished CRT. Patients will continue to be enrolled past the initial safety cohort, but if at any time, safety analysis reveals >2 out of the 8 patients in the safety cohort have developed a DLT, then no further patient may be enrolled to that arm due to excess toxicity with this combination. If the safety event occurs prior to surgery only, than the pre-surgery dose of Pembrolizumab will be discontinued for the following patients but the trial will continue with adjuvant treatment only.

5.2.2.3.1 Dose Limiting Toxicity

Dose limiting toxicity will be defined as any adverse effect, that in the treating investigator's opinion, was felt to be due to Pembrolizumab and significantly delayed standard of care treatment (> 7 days delay in surgery, >3 days for radiation, and/or >7 days for Cisplatin dose). In these patients, Pembrolizumab will be discontinued permanently.

5.2.2.4 Dose Modification

5.2.2.4.1 Pembrolizumab - **Dose Modification and toxicity management for immune-related AEs associated with pembrolizumab and combination therapy**

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 the most current investigator's brochure for supportive care guidelines, including use of corticosteroids.

Table 3

Dose Modification Guidelines for Drug-Related Adverse Events

General instructions:

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

Immune-related AEs	**Toxicity grade or conditions (CTCAE v 4.0)**	**Action taken to Pembrolizumab**	**Immune Related AE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroi d treatment

	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		•
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritonea l signs and ileus). Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/coli tis should be advised

	Grade 4	Permanently discontinue		to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

AST / ALT elevation or Increased bilirubin AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in	• Monitor participants for hyperglycemi a or other signs and symptoms of diabetes.

			participants with hyperglycemia	
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 3 or 4	Permanently discontinue	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer	• Ensure adequate evaluation to

	Grade 2, 3 or 4	Permanently discontinue	corticosteroids	confirm etiology and/or exclude other causes

All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
1. Withhold or permanently discontinue Pembrolizumab is at the discretion of the investigator or treating physician. **NOTE:** For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of Pembrolizumab is required, Pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

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. If a pembro dosed is held, then that dose is considered missed.

5.2.2.4.2 Cisplatin

Use the actual body weight for all patients. There should be no dose modifications because of obesity.

Cisplatin dose can be reduced up to 2 times if AEs occur (1st dose reduction of 25% to 30mg/m2 and then subsequently to 23mg/m2). However, if AEs as listed below continue to occur despite 2 subsequent dose reductions, therapy should be discontinued permanently. Chemotherapy dose should never be escalated.

Neutropenia: If on the day of scheduled treatment with Cisplatin the absolute neutrophil count (ANC) is < 1000/mm3, hold chemotherapy treatment but not the radiation until ANC ≥ 1000/mm3, then treat at 25% dose reduction. 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.

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 75% dose.

Neurotoxicity: If grade 2 neurotoxicity develops, hold Cisplatin (but continue RT) until toxicity improves to < grade 1, then reduce the following Cisplatin dose by 25%. If any signs of grade 3 or greater neurotoxicity occur, discontinue Cisplatin, but continue RT.

Renal Adverse Events: Cisplatin dose should be based on the serum creatinine or creatinine clearance immediately prior to the second and third Cisplatin dose using the following guidelines:

Note: If creatinine is > 1.5 mg/dl, 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:

Serum Creatinine Creatinine Clearance Cisplatin Dose (Dose reductions should be made from current dose level)

≤ 1.5 mg/dl or > 50 ml/min then administer full dose

> 1.5 mg/dl and 40-50 ml/min then administer at 25% dose reduction

> 1.5 mg/dl and < 40 ml/min Hold drug*

*Cisplatin should be held (but the RT continued) and the creatinine measured weekly, until it is < 1.5 mg/dl or the creatinine clearance is > 50 ml/min, and then the next and following doses of Cisplatin should be given at a dose reduction of 25%.

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.

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.

Ototoxicity: For clinical hearing loss not requiring a hearing aid, reduce Cisplatin by 2 dose levels (23mg/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 by 2 dose levels. 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.

Other Toxicities: For any other grade 3-4 adverse events, hold Cisplatin until toxicities have recovered to grade 1 or less. Dose may be reduced by 1 or 2 dose levels for next treatment if felt necessary by discretion of investigator.

If any doses of Cisplatin are skipped due to hematologic, neurologic, renal, or other adverse events, these doses will NOT be made up at end of treatment. Cisplatin will continue only during time of radiation treatment. If a weight change of ≥10% occurs, the following Cisplatin doses should be adjusted.

5.2.3 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). Study Drug may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. Cisplatin should not be delayed more than 1 day of scheduled dose. Pembrolizumab should be given 30 minutes prior to Cisplatin dose on days in which they are administered together.

All trial treatments will be administered on an outpatient basis.

Cisplatin

Cisplatin will be given at 40mg/m2 starting concurrently with radiation one week after first post-surgery Pembrolizumab dose is given. Cisplatin will be given weekly for 6 doses during the radiation treatment. Any skipped doses will not be made up at the completion of radiation therapy.

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

Mechanism of Action: The dominant mode of action of Cisplatin is inhibition of the incorporation of DNA precursors, although protein and RNA synthesis are also inhibited. Although Cisplatin is thought 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 other standard alkylating agents.

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

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

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

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

5.2.4 Surgery

Patients must have undergone gross total surgical resection no earlier than 7 days and no later than 21 days after initial Pembrolizumab administration.

5.2.4.1 Surgical Quality Assurance Reviews

The Surgical Oncology Co-Chair, Keith Casper, MD, will perform a Quality Assurance Review after complete data for the first 20 cases enrolled has been received at UCCC. He will review pathology and operative reports for compliance with eligibility based on documentation of the pathologic descriptors for high-risk disease: extracapsular nodal extension or invasive cancer seen on microscopic evaluation of resection margins. Dr. Casper will perform the next review after complete data for the next 20 cases enrolled has been received at UCCC. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at UCCC, whichever occurs first.

5.3 Stratification

After surgical resection, patients will be stratified into two groups: high risk patients with proven positive surgical margins or extracapsular extension of lymph nodes or intermediate risk including all patients not meeting criteria for high risk. There is a small chance that although patients are identified clinically to require radiation prior to surgery, that the pathology will deem the patient to be low risk and radiation would not be considered standard of care. In the event, the investigator feels it is not in the best interest of patient to administer radiation (or radiation would not be considered standard of care), then patient may be withdrawn from the study.

5.4 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed while on treatment or in end of treatment follow-up period. 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 Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician and decision must be discussed with PI to determine if patient remains eligible to receive treatment.

5.4.1 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.

5.4.2 Prohibited Concomitant Medications

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

- Biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than Pembrolizumab
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids should be avoided if possible. Steroids are allowed as anti-emetic around Cisplatin dosing, as short bursts of 5-7 days if required for clinical indication (ie COPD) or to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The chronic 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 other than specified as allowed, 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.

5.5 Rescue Medications & Supportive Care

5.5.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator.

5.5.1.1 Pembrolizumab

Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below and in greater detail in the investigator's brochure. 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. 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.

- **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** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

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

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

- **Hypophysitis**:

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

	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., 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.

5.5.1.2 Cisplatin

High dose Cisplatin is a highly emetogenic regimen with significant incidence of delayed nausea and vomiting. The following guidelines are suggested:

1. 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. Fosaprepitant may also be included as premedication.

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

3. 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.

5.6 Diet/Activity/Other Considerations

5.6.1 Diet

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

5.6.2 Contraception

Cisplatin is known to be teratogenic and embryotoxic. 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. 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.

5.6.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with Pembrolizumab/Cisplatin, 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 without delay and within 24 hours to the Sponsor if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

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

5.6.4 Use in Nursing Women

It is unknown whether Pembrolizumab is excreted in human milk and there are mixed reports on Cisplatin excretion. 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.

5.7 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
- 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 may be followed by telephone or in person for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8 Subject Replacement Strategy

Patients who are unfit or unwilling to continue study after resection will be replaced. Patients who choose not to undergo surgical resection after initial dose of Pembrolizumab will be replaced. In addition, any patient who does not complete at least 1 week of adjuvant treatment will also be replaced.

5.9 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		Pre-surgery Dose	Surgery	Adjuvant Treatment											End of Treatment	Post-Treatment	
												Post CRT						
Treatment Dose Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2) [P]	Pre-Surgery Dose [P]		1	2	3	4	5	6	7	8	9	10	NA	Discon	Safety Follow-up[n]	Survival Follow-Up[a]
Scheduling Window (Days):	-35 to -7	-22 to -7	-21 to -7	0	28 to 77	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 3	± 3	± 14	At time of Discon[c]	30 days and 3 months post discon	+/- 2 weeks
Adjuvant Treatment (Week):					1	2	3	4	5	6	7	10	13	16	19	(20[d])	20[d]	
Administrative Procedures																		
Informed Consent	x	X[o]	X[o]															
Inclusion/Exclusion Criteria		x																
Demographics and Medical History		x																
Prior and Concomitant Medication Review		x	X		X	X	X	X	X	X	X	X	X	X		X	x	
Pembrolizumab Administration[j]			x		x			x			x	x	x	X				
Cisplatin 40mg/m2 weekly if indicated[b]						x	x	x	x	x	x							
Radiation 2-2.2 Gy Fxs M-F						x	x	x	x	x	x							

Trial Period:	Screening Phase		Pre-surgery Dose	Surgery	Adjuvant Treatment											End of Treatment	Post-Treatment	
												Post CRT						
Treatment Dose Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2) [P]	Pre-Surgery Dose [P]		1	2	3	4	5	6	7	8	9	10	NA	Discon	Safety Follow-up[n]	Survival Follow-Up[a]
Scheduling Window (Days):	-35 to -7	-22 to -7	-21 to -7	0	28 to 77	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 3	± 3	± 14	At time of Discon[c]	30 days and 3 months post discon	+/- 2 weeks
Adjuvant Treatment (Week):					1	2	3	4	5	6	7	10	13	16	19	(20[d])	20[d]	
Post-study anticancer therapy status															x			x
Survival Status															X	X	X	x
Clinical Procedures/Assessments																		
Review Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	x
Full Physical Examination[e]		X													x	x		
Directed Physical Examination					X			X			X	x	x	X			x	
Dental Exam		X[h]																
Dysphagia/Swallowing Function					X[l]													
Vital Signs and Weight		X	X		X	X	X	X	X	X	X	X	X	X		x	x	

Trial Period:	Screening Phase		Pre-surgery Dose	Surgery	Adjuvant Treatment											End of Treatment	Post-Treatment	
												Post CRT						
Treatment Dose Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2) [P]	Pre-Surgery Dose [P]		1	2	3	4	5	6	7	8	9	10	NA	Discon	Safety Follow-up[n]	Survival Follow-Up[a]
Scheduling Window (Days):	-35 to -7	-22 to -7	-21 to -7	0	28 to 77	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 3	± 3	± 14	At time of Discon[c]	30 days and 3 months post discon	+/- 2 weeks
Adjuvant Treatment (Week):					1	2	3	4	5	6	7	10	13	16	19	(20[d])	20[d]	
ECOG Performance Status		x	x		x			x			x	x	x	x	x	x		
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory																		
Pregnancy Test – Urine or Serum -HCG		x																
CBC with Differential[m]		x		x[k]	x	x	x	x	x	x	x	x	x	x		x		
Comprehensive Serum Chemistry Panel[i, m]		x		x[k]	x	x	x	x	x	x	x	x	x	x		x		
Urinalysis		x			x			x			x			x		x		
T3, FT4 and TSH		x		x[k]	x			x			x			x		x		
PT/INR, PTT		x		x[k]	x			x			x			x		x		
Efficacy Measurements																		
Tumor Imaging[f]		x													x			

Trial Period:	Screening Phase		Pre-surgery Dose	Surgery	Adjuvant Treatment											End of Treatment	Post-Treatment	
												Post CRT						
Treatment Dose Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2) [P]	Pre-Surgery Dose [P]		1	2	3	4	5	6	7	8	9	10	NA	Discon	Safety Follow-up[n]	Survival Follow-Up[a]
Scheduling Window (Days):	-35 to -7	-22 to -7	-21 to -7	0	28 to 77	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 3	± 3	± 14	At time of Discon[c]	30 days and 3 months post discon	+/- 2 weeks
Adjuvant Treatment (Week):					1	2	3	4	5	6	7	10	13	16	19	(20[d])	20[d]	
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood																		
Archival or Newly Obtained Tissue Collection[g]		x		x														
Correlative Studies Blood Collection[g]		x		x[k]	x		x											

Trial Period:	Screening Phase		Pre-surgery Dose	Surgery	Adjuvant Treatment											End of Treatment	Post-Treatment	
												Post CRT						
Treatment Dose Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2) [P]	Pre-Surgery Dose [P]		1	2	3	4	5	6	7	8	9	10	NA	Discon	Safety Follow-up[n]	Survival Follow-Up[a]
Scheduling Window (Days):	-35 to -7	-22 to -7	-21 to -7	0	28 to 77	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 3	± 3	± 14	At time of Discon[c]	30 days and 3 months post discon	+/- 2 weeks
Adjuvant Treatment (Week):					1	2	3	4	5	6	7	10	13	16	19	([20d])	[20d]	

a. Patients will be followed every 3 weeks for first 3 months following CRT (post CRT above) and then every 3 months (every 12 weeks) for first 2 years followed by every 6 months (24 weeks) for a total of 5 years. Adjuvant weeks are numbered starting with first Pembrolizumab infusion which should begin 4-11 weeks after resection. FU visits can be conducted by phone if the study subjects will not see a study doctor on those days.

b. Only patients with confirmed high risk features (+ECE and/or + margins) will receive Cisplatin.

c. Time of discontinuation is either after last Pembrolizumab dose which will correspond to safety visit at week 20 or at time that patient discontinues treatment due to side effects, progression or withdrawal of consent.

d. Safety visit will be completed on week 20 unless study discontinued early at which time it should be done at 30 days post-treatment. 30 day safety follow up visit only needed for subjects who withdraw or discontinue the study.

e. Full physical exam only includes full head and neck and fiberoptic exam at week 19 but can be completed between week 11 and 20 to count towards week 19 assessment.

f. Pre-operative scans including chest imaging preferably PET/CT and CT neck + contrast. (CT chest and CT neck + contrast would also be acceptable). If contrast contraindicated, MRI of neck is also acceptable. Post CRT imaging requires a PET/CT or CT of neck and chest.

g. See procedure manual for tissue specifications and tubes required. MDA fresh tissue to be collected per MDA standard.

h. Dental exam to be completed anytime before initiation of radiation.

Trial Period:	Screening Phase		Pre-surgery Dose	Surgery	Adjuvant Treatment											End of Treatment	Post-Treatment	
												Post CRT						
Treatment Dose Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2) [P]	Pre-Surgery Dose [P]		1	2	3	4	5	6	7	8	9	10	NA	Discon	Safety Follow-up[n]	Survival Follow-Up[a]
Scheduling Window (Days):	-35 to -7	-22 to -7	-21 to -7	0	28 to 77	± 1	± 1	± 1	± 1	± 1	± 1	± 3	± 3	± 3	± 14	At time of Discon[c]	30 days and 3 months post discon	+/- 2 weeks
Adjuvant Treatment (Week):					1	2	3	4	5	6	7	10	13	16	19	([20d])	[20d]	

i. See Table 5 for full list.

j. Pembrolizumab to be given 30 minutes before Cisplatin on days administered together.

k. To be drawn before surgery (day of surgery or up to 4 days prior acceptable).

l. This assessment must be performed prior to the start of radiation treatment.

m. For the Radiation and Pembrolizumab arm (intermediate risk), safety labs are not required on non-pembro administration weeks.

n. 3 month post-discontinuation visit is highly recommended, but optional.

o. Informed consent may be obtained on the same day as screening procedures or on the same day as the pre-surgical pembro dose provided the subject has been given a copy of the consent form in advance of this visit to review or adequate time for review on the same-day has been documented.

p. Pre-surgical dose and pre-screening visits may occur on the same day as long as consent is obtained, and eligibility is confirmed prior to prembro dose. All screening labs should be performed within 10 days of treatment initiation (the pre-surgical dose of Pemrolizumab).

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 or clinical coordinator 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/Study Number

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

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit. The screening number will be their study number as well once they are allocated to treatment.

7.1.1.7 Trial Compliance

Interruptions from the protocol specified treatment plan for greater than 3 weeks delay of Pembrolizumab doses, greater than five day delay for radiation treatment or more than 2 skipped doses for Cisplatin treatment require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of trial medication will be witnessed by the investigator and/or trial staff. The total volume of Pembrolizumab infused will be compared to the total volume prepared to determine compliance with each dose of Pembrolizumab administered. The instructions for preparing and administering Pembrolizumab will be provided in the Pharmacy Manual. Treatment with standard therapies will be prepared and administered as per the approved product label.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (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).

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 full physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. Full physical exam only includes full head and neck and fiberoptic exam at week 19 but can be completed between week 11 and 20 to count towards week 19 assessment.

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 at each visit, and at any safety follow-up visits.

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

Imaging will be performed at independent sites and the assessment of response will be determined by independent site investigators.

7.1.2.6.1 Initial Tumor Imaging

Prior to resection all patients should preferably undergo PET/CT and CT neck with contrast. However, chest CT with or without contrast in addition to CT neck with contrast is acceptable.

Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 42 days prior to the first dose of trial treatment.

7.1.2.6.2 Post-Treatment Assessment Imaging

Twelve weeks (+/- 2 weeks) after completion of last radiation treatment (week 19 on flow chart), a PET/CT or CT of neck and chest should be performed to assess for early relapse. Patients will be followed clinically for recurrence after initial post-treatment imaging. No

further imaging is required after initial assessment unless there is suspicion of relapsed disease.

7.1.2.6.3 Assessment of Disease

Patients will be assessed for response 12 weeks after completion of radiation. A full physical exam including head and neck and fiberoptic exam should be performed if indicated per standard of care but not required per protocol every 12 weeks for first 2 years following CRT and then at least every 24 weeks for the next 3 years. For patients felt to have a relapse at any time, a thorough ENT exam as well as a repeat biopsy is recommended to confirm relapsed disease. Follow-up imaging in 4-8 weeks is also acceptable if biopsy is not yet felt to be necessary or is non-diagnostic. Patients will be followed clinically every three months and any concern for relapsed disease or progression should trigger either imaging or biopsy for confirmation. Patients will be followed for relapse for a total of 5 years.

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

Any subjects with oropharyngeal cancers must have documented HPV status (either by p16 or in situ).

Biopsy tissue:

For UC and all Sub-sites: Either a newly obtained core or archival biopsy tissue must be submitted (or determined available and sent at earliest convenience) prior to neoadjuvant Pembrolizumab dose.

For UC only: A biopsy block will be reviewed by the study pathologist (Ben Hinrichs) and retained in the histopathology core. All requests for tissues will be performed per study manual.

For all Sub-sites: Biopsy tissue should be submitted ideally as a block (preferred), or as 25 FFPE slides and 5 tissue scrolls.

For MDA only: Patients, including those with available archival tissue, will have a mandatory fresh biopsy at enrollment. Fresh tissue from biopsy will be processed by the Gillison laboratory using normal procedures for single cell RNA sequencing.

Resection tissue:

For UC only: A resection block will be identified by the study pathologist (Ben Hinrichs) and retained in the histopathology core. All requests for tissues will be performed per study manual. Additional fresh tissue from resection should be collected and submitted per lab manual instructions. Fresh tissue will be prepared and cut by UC Pathology and/or Head and Neck Surgical Team (at least 500mg [0.5cm^3] but if feasible, 2gm [2cm^3] is preferable).

For all Sub-sites: Resection tissue should be submitted as a block (preferred), or as 25 FFPE slides and 5 tissue scrolls from all sub-sites.

For MDA only: Fresh tissue from resection will also be collected. Fresh tissue from resection collected from MDA will be processed by the Gillison laboratory using normal procedures for single cell RNA sequencing.

Blood samples will be collected pre-dose of pre-surgical Pembrolizumab, immediately prior to resection, pre-dose first adjuvant Pembrolizumab dose and on adjuvant week 3 pre-dose of Cisplatin.

Detailed processing, shipping and handling will be provided in the procedures manual.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table5.

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	Total thriiodothyronine (T3)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Free tyroxine (T4)
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Thyroid stimulating hormone (TSH)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	
Absolute Lymphocyte Count	*(O_2 or biocarbonate)*	Urine pregnancy test †	Prothrombin time PT/INR

	Uric Acid		Partial Thromboplastin Time (PTT)
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Creatinine		
	Magnesium		
	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 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.

7.1.3.2 Pharmacodynamic Evaluations

7.1.3.2.1 Peripheral Blood Monocyte Cell (PBMC) Isolation

40 mls of whole blood will be collected in purple top EDTA tubes at 4 timepoints prior to Pembrolizumab administration (on day -28-6 before resection), on day of resection (day 0), prior to Pembrolizumab administration on adjuvant week 1, before 2nd chemotherapy (Cisplatin) and radiation on week 3 (see study calendar) and transferred at room temperature within 24 hours to UCCC.

PBMCs and plasma will be separated by Ficoll centrifugation at UCCC. Plasma will be frozen and stored at -80^{o}C. PBMCs will be either cryopreserved or immediately processed for flow cytometry and functional analysis. Stored plasma will be used for cytokine assays. Please see procedure manual for full details.

7.1.3.2.2 Immunohistochemistry/Immunofluorescence/RNA In Situ Hybridization

Archived biopsy and resected tissue and if fresh resected tissue (Cincinnati only) will be shipped to University of Cincinnati for analysis. FFPE and Frozen sections will be used to analyze the immune cell phenotype (markers include but are not limited to CD4, CD8, PD-1, FOXP3, A2aR, PD-L1, CD73).

7.1.3.2.3 Genomic Analysis

When sufficient tissue is available, FFPE sections may be analyzed by RNA Sequencing and/or next generation whole exome sequencing to understand change in molecular pathways and/or prognostic genetic modifications as well as potential predictors of treatment response. At MDA, fresh biopsy and resection tissue will be used for single cell RNA seq analysis.

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.

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

Potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Visit requirements are outlined in Section 6.0 – Trial Flow Chart. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose trial treatment except for the following:

- Laboratory tests and ECOG PS are to be performed within 10 days prior to the first dose of trial treatment.
- For women of reproductive potential, a serum pregnancy test will be

performed within 72 hours prior to the first dose of trial treatment. A urine test may be considered if serum test is not appropriate.

- Archival or newly obtained tumor collection is required to be obtained within 28 days prior to the first dose of trial treatment.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria and they have not yet started treatment, however, re-screening tests will not be covered by study. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met.

7.1.5.2 Treatment Period

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

7.1.5.3 Post-Treatment Visits

7.1.5.3.1 Safety Follow-Up Visit

If subjects do not discontinue or withdraw early:

- The mandatory Safety Follow-up Visit should correspond to approximately a week after the post-treatment imaging (week 19) on week 20's End of Treatment/Discontinuation visit.

If subjects discontinue or withdraw early:

- 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.

For all subjects, 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 will receive the follow-up PET/CT or CTs as outlined in flowchart in section 6.0. If subjects have no detectable relapse, they will complete the week 20 Safety Follow-up Visit (End of Treatment), and then they will move into the follow-up (post-treatment) stage of the study. Subjects will have follow-up visits every 3 months (12 weeks) either in person at a doctor visit or by phone (if being seen by outside oncologist) for the first 2 years and then every 6 months (24 weeks) for the next 3 years to monitor for relapse, or until time of

withdrawal of consent, or death, whichever comes first. Phone calls are an acceptable form of follow up for all subjects regardless if they are in the care of a local or outside oncologist. If subjects develop a relapse, they will continue to be followed at the time-points described in the flowchart in section 6.0. Every effort should be made to confirm relapse if suspected. During the follow up period, the follow up and survival follow up visits can be calculated in months rather than weeks in order to avoid potential protocol deviations with the scheduling window.

If patients have relapsed disease at time of post-treatment imaging, they should have follow-up imaging at discretion of investigator and, in addition to mandated 30-day safety follow-up, move into survival follow-up.

7.1.5.4.1 Survival Follow-up

Once a subject experiences confirmed disease relapse/progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone, if seen by an outside oncologist, every 3 month (12 weeks) for the first 2 years and then every 6 months (24 weeks) for the next 3 years to assess for survival status until death, withdrawal of consent, or at 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.

If any adverse events related to study drug, pembrolizumab continue after the 30 days post treatment, they should be followed until resolution and/or if they are ongoing at the end of the follow up period, they should continue to be followed per standard of care per their MD.

New SAE/AE's are to be collected and documented in the study EDC during follow up (past 30 days following cessation of treatment) only if they are found to be related to study drug, pembrolizumab.

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)

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). ECIs identified 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, 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) regardless of attribution to study treatment, consistent with standard SAE reporting guidelines. 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:

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

8.1.1 Safety Analysis

The All-Patients-as-Treated (APaT) population will be employed for safety analyses. The safety endpoints are all adverse events graded from 1 to 5. Fisher's exact test will be used to compare the proportion of adverse events among patients treated by Pembrolizumab + radiotherapy in this study with historical patients treated by radiotherapy only and compare patients treated by Pembrolizumab + radiotherapy + Cisplatin in this study with historical patients treated by radiotherapy + Cisplatin. Both the adverse events by grade as well as severe adverse event (SAE; yes/no) will be analyzed. RTOG 9501 data will be used for historical controls using targeted rates of 50% for CRT and 39% for RT. We expect that the addition of Pembrolizumab will not add undue toxicity over standard treatment and therefore, will give insight to the development of future trials.

8.1.2 Efficacy Analysis

All patients who received ≥1 dose of Pembrolizumab will serve as the primary analysis population in this study. The primary efficacy endpoint is to estimate the disease-free-survival (DFS) (i.e., time from treatment allocation to documented first relapse) at 1 year and 3 years. Key secondary efficacy endpoints include overall survival (OS) (i.e., time from treatment allocation to death due to any cause) at 1 year and 3 years. After resection, patients will be stratified based on adverse risk features. Kaplan-Meier method will be used to estimate survival rates for DFS and OS at 1 and 3 years. The survival rates will be compared with historical censored data (RTOG 9501: 66% in CRT and 58% in RT) using the log-rank test.

We will use estimates of the 95% CI for RTOG 9501 for DFS at 1 and 3 years (see below obtained from RTOG), in order to compare our results.

Study Group	RTOG 9501	
	RT Intermediate Risk	CRT High Risk
Disease Free Survival 1 year (95%CI)	68.8% (59.4%-78.2%)	65.4% (57.1%-73.6%)
Disease Free Survival 3 year (95%CI)	44.1% (34%-54.2%)	45.5% (36.9%-54.2%)

We would expect that adding Pembrolizumab would increase the DFS above these rates in RTOG 9501 and that our results would not fall outside of the lower bound of the CI above.

8.1.3 Power and Sample Size

Based upon RTOG 9501, we expect that DFS at 1 year and 3 years will be 65.4% and 53.5% respectively for patients with high risk features undergoing CRT. We expect to reach similar DFS in this study. We expect that at least 50% of patients (~40 patients) based on defined inclusion criteria will have high risk disease confirmed at resection (+ECE or + margins). With an expected sample size of at least N=40 in the CRT arm, and adding Pembrolizumab to Cisplatin and radiation, we expect to reach over 80% power to detect an increase of 21% in DFS at year 1 (86% DFS compared to 65% at 1 year) using the one-sample exact test at significance level, alpha=0.025 (one-sided). In comparison, assuming that we will reach a similar 1 year DFS of 68.8% in the radiation alone arm, by adding Pembrolizumab, and assuming N=40, we expect to reach over 80% power to detect an increase of 19% in DFS at 1 year (88% DFS compared to 69% at 1 year). Every effort will be made to ensure that we have 40 patients either reached the DFS endpoints or were followed for at least one year without disease recurrence in both strata.

8.1.4 Accrual Rate

At the University of Cincinnati, we see approximately 150 new cases of surgically treatable (oral cavity, larynx, hypopharynx) stage III/IV HNSCC per year. Of those, approximately 100% oral cavity, > 50% larynx, and 50% hypopharynx receive surgical resection and about 40%

require adjuvant therapy. We therefore, expect to accrue approximately 1-2 patients per month at UC. Per discussions with our other sites (OSU, Univ of Louisville, MUSC, USCD and Univ of Mich, MD Anderson) we expect to add ~ 1-2 patients a month from each as well. Therefore, we expect enrollment for this phase II study to be completed within 1 year based on 80 patients.

8.2 Statistical Analysis Plan

8.2.1 Safety Endpoints

The safety endpoints are all adverse events graded from 1 to 5 described in Section 7.

The Lead-in population will be assessed for DLTs as described in section 5.2.2.3.1.

8.2.2 Efficacy Endpoints

Primary Endpoint

Disease Free Survival (DFS): measured from the time of treatment allocation to the time of discovery of the first evidence after treatment of any tumor (local, regional, metastatic, or second primary) or death from any cause. DFS at 1 and 3 years will be the primary efficacy endpoints.

Secondary Endpoints

Overall Survival (OS): defined as the time from randomization to death due to any cause. Subjects without documented death at the time of the final analysis will be censored at the date of the last follow-up. OS at 1 and 3 years will be used as secondary endpoints.

Locoregional Control: failure was defined as the reappearance of tumor in the original tumor bed or the development of cervical-node metastases after treatment.

Biomarker analysis including proportion of T cell population subsets before and after immunotherapy both in tumor tissue and peripheral blood.

Exploratory Endpoints

Change in serum cytokines and T cell functionality before and after immunotherapy. DFS and OS will also be measured at 5 years similar to above.

8.2.3 Analysis Population

8.2.3.1 Safety Analysis Population

The All Patients as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all subjects who received at least 1 dose of study treatment. Only those patients who continue treatment after resection will be compared to RTOG 9501 historical controls. Those who receive only pre-resection Pembrolizumab will still be analyzed for safety but there will be no direct comparison. Subjects will be included in the treatment group corresponding to the trial treatment they actually received for the analysis of safety data. Subjects who take incorrect trial treatment for the entire treatment period will be included in the treatment group corresponding to the trial treatment actually received. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of trial treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.2.3.2 Efficacy Analysis Population

The analysis of primary efficacy endpoints are based on all patients who received ≥1 dose of Pembrolizumab. Subjects will be included in the treatment group to which they are stratified after resection.

8.2.4 Statistical Methods

8.2.4.1 Safety Analysis

Descriptive statistics will be provided for safety endpoints. Exact test will be used to compare patients treated by Pembrolizumab + radiotherapy in this study with historical patients treated by radiotherapy only (targeted rate of grade 3 and 4 adverse effects is 39%) and compare patients treated by Pembrolizumab + radiotherapy + Cisplatin in this study with historical patients treated by radiotherapy + Cisplatin (targeted rate of grade 3 and 4 adverse effects is 50%).

8.2.4.2 Disease Free Survival

Kaplan-Meier method will be used to estimate the disease free survival rates at 1, 3 and 5 years among patients treated with combined Pembrolizumab, radiation therapy and +/- Cisplatin. 95% CI of these rates will be provided. These survival rates at 1 year will be estimated and compared with historical data (RTOG 9501: 65.4% in CRT and 68.8% in RT) via the one-sample exact test, point and confidence interval estimation. We will also use the log-rank test and Cox model to compare the DFS between the trial data and the historical data if patient level data obtained from RTOG 9501. An interim analysis will be done throughout study at the PI and statistician discretion.

8.2.4.3 Overall Survival

Kaplan-Meier method will be used to estimate the overall survival rates at 1, 3 and 5 years among patients treated with combined Pembrolizumab, radiation therapy and +/- Cisplatin. 95% CI of these rates will be provided. These survival rates will be compared with historical data using the log-rank test. We will also use Cox model to compare the historical data if patient level data obtained from RTOG 9501.

8.2.4.4 Biomarker Assessments

All biomarker measures will be summarized with descriptive statistics, i.e., percentages for categorical outcomes and means/medians for continuous outcomes, with corresponding standard errors and 95% confidence intervals. Responses will be tabulated by determined response and toxicities will be tabulated by type and grade. For IHC, the percentage of positive cells per area will be multiplied by the staining intensity for each tumor to determine quantitative expression pre- and post-treatment; a 25% change in expression will be considered a positive response. We will use descriptive statistics and graphical displays to evaluate change in serum markers and flow cytometry markers between pre- and post-treatment.

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
Cisplatin 10mg	Lyophilized Powder for Injection

The Cisplatin will be supplied by commercially available product.

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 investigational pharmacy (if used per site) 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.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

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

10.1.1 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

10.1.2 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all sub-investigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:
1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information.

Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

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

10.2 Compliance with Financial Disclosure Requirements

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

Disclosure information is required. It is the investigator's/sub-investigator's responsibility to comply with any such request.

10.3 Compliance with Law, Audit and Debarment

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

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

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

10.6.1 Data Storage

Data collection and storage will be managed by the University of Cincinnati Cancer Center, Clinical Trials Office (UCCC CTO). The UCCC CTO will maintain storage of all clinical data in accordance with federal guidelines and GCP. Data will be entered in a secure, password protected storage database, OnCore and/or RedCap. All hardcopies of data will be securely maintained (in a locked room or cabinet) and will only be accessible to members of the study team.

10.6.2 Data and Safety Monitoring

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

Any new significant finding that may affect the patient's willingness to continue in the study will be shared with patients. Immediately after the study is approved and before the first patient is enrolled, investigators will meet, develop and finalize all measurements/variables for the study. Each patient, once enrolled, will be provided a unique ID for the study. Personal information, such as name, SSN, address, phone number and DOB, will be de-identified. Confidentiality will be maintained during the phases of the trial including monitoring, preparation of interim results, review, and response to monitoring recommendations. Exceptions may be made under circumstances where there are serious adverse events or when it is deemed appropriate for patient safety.

Study progress will be monitored regularly by the UCCC Data Safety Monitoring Board (DSMB). Membership consists of persons independent of, and without any conflicts of interest with, this trial. The DSMB includes experts in the fields of relevant clinical expertise (oncology) and biostatistics.

It is the responsibility of the sponsor-investigator to ensure that the DSMB is apprised of all new safety information relevant to the study IND and the study. Study progress & safety information will be prepared by the DSMB Coordinator with input from the PI as to the current status of the trial. This compiled information presented to the DSMB will include: a narrative summary from the PI as to trial progress and identification of any trends of significance or explanation of any SAEs or other safety related events; the accrual rate with projected completion date for the accrual phase; exclusion rates and reasons; pretreatment characteristics of patients accrued when relevant; and, the frequency and severity of adverse events.

The DSMB will function in an advisory capacity and recommendations/requests from the DSMB will be reviewed by the sponsor-investigator and promptly addressed.

The study data from participating sub-sites will be reviewed remotely via RedCAP and in person by the Study Monitor as per the Clinical Monitoring Plan (Plan kept on file with UCCC CTO office).

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)

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