PROTOCOL AMENDMENT # 2

LCCC 1509: Pembrolizumab and Radiation for Locally Advanced Squamous Cell Carcinoma of the Head and Neck (SCCHN) not Eligible for Cisplatin Therapy

AMENDMENT INCORPORATES:

X Editorial, administrative changes
X Scientific changes (IRB approval)
Therapy changes (IRB approval)
X Eligibility Changes (IRB approval)
Other

Summary of Changes

- Updated the following sections of the protocol to align with the most recent dose modification and guidelines recommended for Merck protocols: Inclusion criteria 3.1.9 and 3.1.10; Added section 5.1.8 – Contraception which provides details on acceptable methods of birth control for WOCBP and males on the study; also updated sections 4.3.3, 4.3.4, 4.4.1, 4.4.2, 5.1.11, 7.1.1, 7.1.4, and 7.3.3. Section 7.1.5 was deleted.

The attached version dated September 02, 2016 incorporates the above revisions

LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

PROTOCOL AMENDMENT # 1

LCCC 1509: Pembrolizumab and Radiation for Locally Advanced Squamous Cell Carcinoma of the Head and Neck (SCCHN) not Eligible for Cisplatin Therapy

AMENDMENT INCORPORATES:

X Editorial, administrative changes
X Scientific changes (IRB approval)
Therapy changes (IRB approval)
X Eligibility Changes (IRB approval)
Other

Summary of Changes

- Added 3.2.17 criterion to exclude subjects with a history of non-infectious pneumonitis because pneumonitis is an identified risk of pembrolizumab therapy.
- Checks for respiratory signs/symptoms + respiratory history were added to Evaluations and Assessments in section 6.0 of the protocol. Ongoing patients are to be evaluated for active pneumonitis. Patients with a history of pneumonitis should be re-consented for this trial to consider if they should continue pembrolizumab or discontinue treatment based on the risk of fatal pneumonitis reported in recent safety findings.
- Updated protocol in sections 1.1 and 1.9 to allow subjects in LCCC1509 to co-enroll in LCCC1108

The attached version dated July 29, 2016 incorporates the above revisions

LCCC 1509: Pembrolizumab and Radiation for Locally Advanced Squamous Cell Carcinoma of the Head and Neck (SCCHN) not Eligible for Cisplatin Therapy

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name:_____

PI Signature: _____

Date:

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1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

We plan to enroll 29 patients in this open label, single arm, phase II study of the humanized monoclonal antibody (mAB) targeted against cell surface receptor programmed cell death-1 (PD-1), pembrolizumab, concomitant with and following standard of care definitive radiation for locally advanced SCCHN patients who are not good candidates for cisplatin. We hypothesize that treatment with pembrolizumab and standard definitive radiation will result in a median progression free survival (PFS) of 16 months, superior to a historic control of 10 months. Secondary endpoints include PFS at 20 weeks, 1 year and 2 years, objective response rate (ORR: complete response (CR)+ partial response (PR)), rate of CR, overall survival (OS), time to locoregional recurrence and time to distant metastases. We will also characterize the toxicity profile of the treatment and describe quality of life over the course of therapy.

We may perform Multiplex next generation sequencing of DNA and RNA for expression profiling and protein-level analysis for expression level of checkpoints that could influence the efficacy of pembrolizumab via co-enrollment of LCCC1509 patients into a separate tissue procurement study LCCC1108. These studies may allow us to explore associations between these immuno-based correlatives with clinical outcome.

It is standard of care to evaluate Human Papillomavirus (HPV) status in all oropharynx SCCHN patients, and we will also explore association between HPV status and outcome.

1.2 Locally Advanced SCCHN: Cisplatin and Radiation as Standard of Care (SOC)

The most common treatment of locally advanced SCCHN is the concomitant use of cisplatin and radiation. This "bolus" or "high dose" regimen consists of daily (Mon-Fri) radiation for 7 weeks, and cisplatin 100mg/m^2 IV given every three weeks for a total of 3 doses starting day 1 of radiation. This combination is highly accepted both in the United States and internationally as a result of several studies. Two such studies were particularly important. The meta-analysis of chemotherapy in head and neck cancer (MACH-NC) [1] included all trials completed at the time of analysis that compared loco-regional treatment alone to loco-regional treatment plus chemotherapy (n >16,000 patients), whether chemotherapy was given prior to (induction), concomitant with, or post local treatment. The greatest benefit was seen when chemotherapy was given concomitantly with radiation with a hazard ratio (HR) of 0.81 compared to loco-regional treatment alone. High dose single agent cisplatin was the most active chemotherapy agent, and the only drug recommended to be used alone when combined with definitive (i.e., curative intent) radiation. The second study, RTOG 91-11[2] was designed as a larynx-preservation trial, but its findings have

been widely applied to other SCCHN anatomic sites as well. In this study, patients with locally advanced larynx cancer were randomized to induction chemotherapy followed by radiation, to concurrent chemoradiation or to radiotherapy alone. The chemotherapy used in the chemoradiation arm of this trial was high dose cisplatin. Five-year disease free survival (DFS) improved from 27% with radiation alone to 36% with the addition of cisplatin, while overall survival (OS) at 5 years was unchanged. These results are inadequate on an absolute basis, but are particularly unimpressive when toxicity is accounted for—82% of patients on RTOG91-11 experienced severe toxicity.

1.2.1 High-dose bolus Cisplatin with Radiation Therapy: A Standard of Care that roughly half of patients cannot receive

Despite being the "standard" regimen, a large proportion of patients are not eligible for high-dose bolus cisplatin. Cisplatin is very ototoxic, and therefore poses increased risks to patients with any pre-existing high-frequency hearing loss or tinnitus. Its high degree of nephrotoxicity is of particular concern for patients with any pre-existing renal insufficiency, diabetes, or other risk factors for renal problems. Cisplatin is highly neuropathic and therefore contraindicated in patients with pre-existing neuropathy and considered high risk in patients with diabetes. Cisplatin is highly emetogenic; therefore, after appropriate counseling, many patients refuse it and many clinicians prefer to avoid it for patients with borderline performance status (PS).

1.3 Locally Advanced SCCHN: Alternative Regimens

Given the many problems with high dose cisplatin, it is surprising that there is no well-accepted, well-validated alternative. The most frequently used alternative to high-dose cisplatin is weekly cisplatin. At a dose of 20mg/m^2, the existing data indicates a lack of efficacy[3]. At a dose of 40mg/m^2, limited data suggest efficacy, but the toxicity starts to approach that of high dose cisplatin[4]. A mid-range dose of 30mg/m^2 weekly is very commonly used, but data on efficacy are very limited and it is not clear if this regimen is better than radiation alone or as good as bolus cisplatin[5, 6]. None of these weekly regimens have ever been compared head to head with either radiation alone or with bolus cisplatin in a phase III randomized study.

Perhaps the best-validated alternative regimen is weekly cetuximab combined with radiation, approved for this indication by the FDA in 2006. Cetuximab is a monoclonal antibody against the epidermal growth factor receptor (EGFR). A single randomized study comparing radiation combined with cetuximab to radiation alone [7, 8] demonstrated superior locoregional control, PFS and OS for the combination arm; the rate of distant metastases was not improved. Cetuximab, however, is not widely used for a variety of reasons: concerns that it may be less effective than cisplatin, risk of anaphylaxis and controversy regarding subgroup analyses from the Bonner trial. Subgroup analysis from the Bonner study demonstrated that benefit was driven by patients with characteristics that describe the HPV+ population: young male patients with good performance status

(PS) and oropharynx primary site [7, 8]. However, HPV+ tumors tend to be low expressers of EGFR [9] and, when final HPV data became available, there was no preferential effect by HPV [10]. Novel agents for the treatment of locally advanced SCCHN are needed. Anticancer immunotherapeutics represent one exciting new class of novel agents worthy of further study in SCCHN.

1.4 Pembrolizumab (MK-3475)

Pembrolizumab (MK-3475) is a potent and highly selective intravenous humanized mAb of the immunoglobulin (Ig) G4/kappa isotype that directly blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate an antitumor immune response, leading to tumor regression and immune rejection of the tumor. Indications currently under investigation by the manufacturer of pembrolizumab include non-small cell lung cancer and glioblastoma. Keytruda™ (Pembrolizumab) has recently been approved (at a dose of 2 mg/kg IV every 3 weeks) in the United Stated for the treatment of patients with unresectable or metastatic melanoma with disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor. Further development of pembrolizumab in non-metastatic melanoma is ongoing.[11]

1.4.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [12]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [13-17]. 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 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [18, 19]. The structure of murine PD-1 has been resolved [9]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM).

Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70, all of

which are involved in the CD3 T-cell signaling cascade [18, 20-22]. 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 [13; 14]. PD-1 is expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells [23, 24]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [25].

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 [25-28]. Both ligands are type I transmembrane receptors containing both IgV- and Ig (constant) C-like domains in the extracellular region and 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 [29]. Although healthy organs express little (if any) PD-L1, a variety of cancers are known 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) [30]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

1.4.2 Pre-clinical Findings

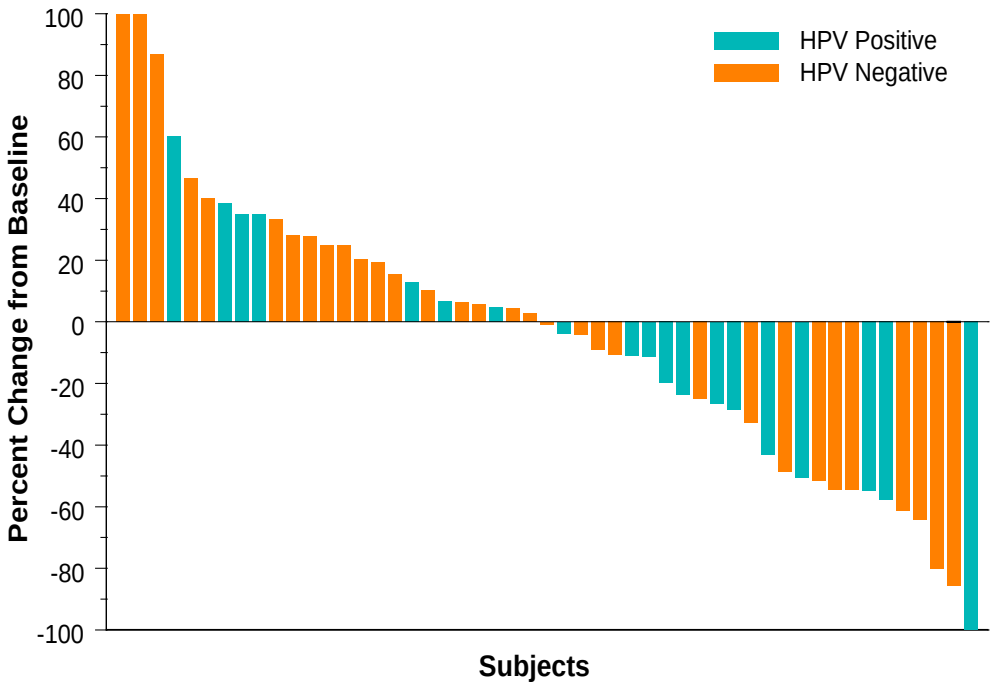
Pembrolizumab strongly enhances T-lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. In T-cell activation assays using human donor blood cells, the EC50 (concentration where 50% of the maximum effect is achieved) has been reported to be ~0.1 to 0.3 nM. Levels of interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), and other cytokines are modulated by MK-3475. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T-cells.[11]

Using an anti-murine PD-1 analog antibody, PD-1 blockade has been shown to significantly inhibit tumor growth in a variety of syngeneic murine tumor models. In these experiments in mice, anti-PD-1 therapy is synergistic with chemotherapeutic agents such as gemcitabine and 5-fluorouracil (5-FU) and combination therapy results in increased complete tumor regression rates in vivo.[11]

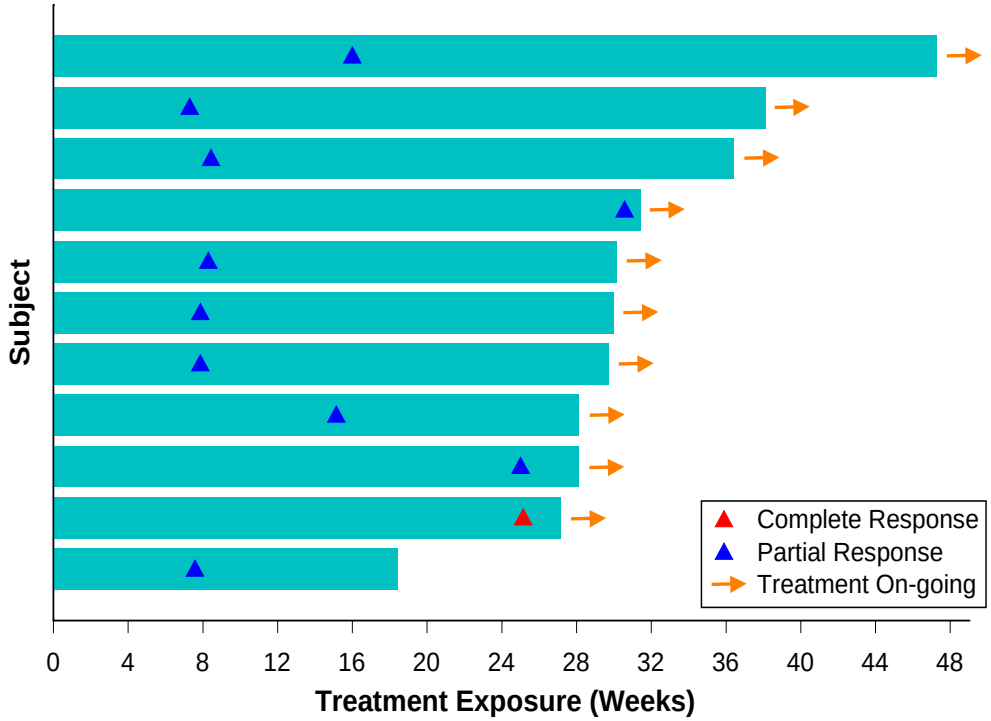
The safety of MK-3475 was characterized in the 1-month repeat-dose toxicity study in cynomolgus monkeys when administered as intravenous (IV) doses of 6, 40 or 200 mg/kg once a week (a total of five doses) and in the 6-month repeat-dose toxicity study in the same species when administered as IV doses of 6, 40 or 200 mg/kg every other week (a total of 12 doses). MK-3475 was well-tolerated with a systemic exposure (area under the curve (AUC)) of up to ~170,000 µg/day/mL over the course of the 1-month study, and with an AUC of up to approximately 67,500 µg.day/mL over the course of the 6-month study. No findings of toxicological significance were observed in either study and the No Observed Adverse Event Level (NOAEL) was ≥200 mg/kg. In addition, no findings of toxicological relevance were observed in the in vitro tissue cross-reactivity study using human and cynomolgus monkey tissues.[11]

1.5 Clinical Efficacy of PD1 Inhibition in Human SCCHN

Pembrolizumab is very active against human SCCHN. In a Phase Ib study of recurrent/metastatic SCCHN, pembrolizumab demonstrated a 20% response rate in both HPV+ and HPV- patients [31], as evidenced in the water-fall plot below.



Some of these responses seemed durable:



Additional experience in other cancers confirms the activity and tolerability of pembrolizumab [32, 33]

1.5.1 Clinical Safety of Pembrolizumab in SCCHN

For the average patient, pembrolizumab is quite nontoxic as the adverse event data (AEs: table summarizes those with a ≥ 5% incidence) from the head/neck phase Ib expansion cohort as shown below [31]:

Adverse Event	All Grades Drug-related		Grade 3-5 Drug-related	
	n	(%)	n	(%)
Any Adverse Event	35	(58.3)	10	(16.7)
Fatigue	10	(16.7)	0	(0.0)
Pruritus	6	(10.0)	0	(0.0)
Rash	4	(6.7)	1	(1.7)
Nausea	4	(6.7)	0	(0.0)
Decreased appetite	3	(5.0)	0	(0.0)
Myalgia	3	(5.0)	0	(0.0)

1.6 Radiation and Immunology

Radiation therapy may act, at least in part, through immunologic mechanisms.

Radiation can lead to tumor cell death and subsequent antigen exposure. It has long been hypothesized that the abscopal effect (when one tumor location is treated with radiotherapy and tumor at a separate location regresses) is caused through an immunotherapeutic mechanism. Recently, this hypothesis was tested in a mouse model in which tumor was injected into both flanks of the mice. When only one flank was irradiated, there was no growth inhibition of the contralateral flank but when PD-L1 inhibition was added, there was growth inhibition. [34]

In vitro data also suggest that fractionated radiation increases tumoral PD-L1 expression. [34, 35] Inhibition of PD-1 or PD-L1 concurrently with radiation enhances radiation sensitivity and increases the cure rate in mice treated with radiotherapy[34]. Treatment with radiotherapy and PD-L1 inhibition leads to tumor antigen specific memory T cell responses that are protective against repeat tumor challenge. Given the high rates of recurrence and second primary head/neck cancer, these results are potentially important to the treatment of human cancer.

1.6.1 Radiation Safety in SCCHN

In the Bonner trial cited earlier, the adverse events that occurred in at least 10% of patients (any grade) in the radiotherapy treatment arm alone included the following: mucositis (94%); rash (10%); radiation dermatitis (90%); weight loss (72%); xerostomia (71%); dysphagia (63%); asthenia (49%); nausea (37%); constipation (30%); taste perversion (28%); vomiting (23%); pain (28%); anorexia (23%); fever (13%); pharyngitis (19%); dehydration (19%); oral candidiasis (22%); coughing (19%); voice alteration (22%); diarrhea (13%); insomnia (14%); increased sputum (15%); and anemia (13%). The potential overlapping toxicities with pembrolizumab (nausea, diarrhea and rash) were, with rare exception, $\leq$ Grade 2. The $\geq$ Grade 3 adverse events that occurred in at least 10% of patients in the same arm included: mucositis (52%); radiation dermatitis (18%); and dysphagia (30%).

1.7 Safety of Pembrolizumab Combined with Radiation

Several patients in ongoing clinical trials have been treated with pembrolizumab and radiation. The first (NCT02305186), a Phase I/II study, randomizes patients with borderline resectable pancreatic cancer to fixed dose radiation (50.4 Gy total over 28 daily fractions) and capecitabine (825mg/m^2 twice daily on the days radiation is due) with or without concomitant pembrolizumab 200mg IV every 3 weeks. A second Phase II trial (NCT02289209) is enrolling locoregional inoperable recurrent or second primary SCCHN patients to pembrolizumab 200mg IV every 3 weeks concomitant with 1.2 Gy radiation twice daily, 5 days a week for 5 weeks.

Safety data is pending from these studies. However, the most frequent toxicities associated with pembrolizumab including low grade nausea, cough, pruritis, diarrhea and rash should not overlap with the major toxicities of radiation, and the

mechanisms of action are distinct (meaning we expect no more than additive toxicity). Therefore, no serious safety issues are anticipated as a result of this combination. Any unexpected toxicities from the ongoing studies just summarized will be shared with the PI of LCCC1509 by the manufacturer of pembrolizumab and can be used to supplement toxicity monitoring if needed.

In this trial, toxicity will be monitored continuously, with sequential boundaries employed to suspend the trial if excessive numbers of patients fail to receive at least 95% of the intended dose of radiation (8.3). If the study reaches a stopping boundary, it may be terminated by the PI, or submitted to the DSMC with a description of the toxicities and a rationale for why the study should be continued.

1.8 Rationale

In summary, there is no accepted standard of care agent to be given together with radiation for patients who are not eligible for cisplatin. As a result, the clinical research community has accepted the appropriateness of conducting trials of novel agents with radiotherapy. NCT01540682, NCT 00736619, NCT 01386632, NCT 01946867 and NCT 00206752 serve as examples of the acceptability of clinical trials in this setting. Further, surgical salvage has always been a standard part of treatment for locally advanced head/neck cancer and would remain so in any novel paradigm. In RTOG91-11 referenced above, a high proportion of patients in each arm had residual or recurrent disease, but had salvage surgery for cure. This surgical salvage option further enhances the safety of novel combined modality radiation strategies.

1.8.1 Rationale for Pembrolizumab Schedule

When chemotherapy is given together with radiation therapy for locally advanced head and neck cancer, the standard sequencing is concurrent treatment [1, 2, 36]. As reviewed in section 1.2, the standard regimen for chemotherapy when administered concurrent with radiation is high-dose cisplatin administered every three weeks. The standard schedule of pembrolizumab is also every three weeks (see section 1.8.2 for additional data) and this has therefore been maintained.

Historically, adjuvant therapy has not been efficacious, although it has never been studied with modern agents. Studies of neo-adjuvant treatment have focused on TPF (docetaxel, cisplatin and 5FU) where results have been negative [37-39] although the question is being re-asked with more modern agents (for example NCT01412229). Because existing data on pembrolizumab indicate that efficacy can be delayed, it would be reasonable to utilize neo-adjuvant pembrolizumab or to at least to start pembrolizumab before radiation. Such an approach might improve efficacy, but would also delay the initiation of radiation. This approach is worthy of study, but is outside the context of this study of concurrent therapy.

Cell death from radiation is known to continue for weeks after the conclusion of active therapy; for this reason, we chose to administer additional pembrolizumab cycles after the conclusion of radiation. Given the lack of overlap between

pembrolizumab toxicity and the typical side effects of radiation that patients will be recovering from at this time point, we believe that the relative ratio of potential benefit of this approach vastly exceeds the risk of harm.

1.8.2 Rationale for Dose Selection of Pembrolizumab

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

Pharmacokinetic (PK) data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life. [11] Pharmacodynamic (PD) data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and PD data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population PK analysis of pembrolizumab has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and supports both body weight normalized dosing or a fixed dose across all body weights (Merck, written communication).

The choice of the 200 mg every 3 weeks as an appropriate dose for the switch to fixed dosing of pembrolizumab (which is pending FDA approval, and which is incorporated into this study) 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 (the current FDA approved dose), 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 (Merck, written communication). A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

1.9 Correlative Studies

It is standard of care to evaluate HPV status in all oropharynx SCCHN patients seen at UNC and sites recruited to participate will be required to obtain HPV status, and we will explore association between HPV status and outcome.

Exploratory objectives based on serial blood collections and tumor samples may include some or all of the following (depending on availability of archival diagnostic tissue): an evaluation of the predictive capacity of PD-L1 expression, immune gene signatures, and a characterization of the change in phenotype in tumor-infiltrating lymphocytes (TILs) before and after therapy. We may also explore whether T cell and B cell repertoires (TCRs and BCRs respectively; discovered via DNA and RNA sequencing) are enriched in tumors and/or blood at baseline and whether any change is seen in blood post treatment. We hypothesize that each of the following (increased PD-L1 mRNA expression, effector immune infiltrate, clonality in TILs and decreased regulatory cell populations) will be associated with a longer PFS. Collection of samples for correlative studies will be an option provided to patients in LCCC1509 and will involve co-enrollment into the tissue procurement study LCCC1108. We will also collect serum for exploration of a proteomic immune signature under development, and its possible association with OR, PFS and OS. This proteomic immune signature is under development by Biodesix.

Additional details regarding correlative studies can be found in the laboratory manual.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

Estimate PFS after initiation of pembrolizumab (to be administered both concurrent with and following treatment with standard radiation) in locally advanced SCCHN patients not eligible for high-dose bolus cisplatin.

2.2 Secondary Objectives

2.2.1 Evaluate the safety of the proposed regimen by:

- Estimating the proportion of patients who receive <95% of the intended dose of radiation (i.e., <67 Gy)[2]
- Documenting any clinically relevant toxicity (both observer related and patient reported) related to concurrent radiation plus pembrolizumab

2.2.2 Estimate ORR after initiation of pembrolizumab concurrent with and following standard radiation

2.2.3 Estimate rate of CR after initiation of pembrolizumab concurrent with and following standard radiation in locally advanced SCCHN

2.2.4 Estimate OS after initiation of pembrolizumab (to be administered concurrent with and following standard radiation) in locally advanced SCCHN

2.2.5 Estimate time to locoregional recurrence after initiation of pembrolizumab (to be administered concurrent with and post standard radiation)

2.2.6 Estimate time to distant metastases after initiation of pembrolizumab (to be administered concurrent with and post standard radiation)

2.2.7 Describe quality of life over the course of therapy

2.3 Exploratory Objectives

2.3.1 Explore association between HPV status with OR, OS and PFS

2.3.2 To explore the association of biological markers at baseline including PD-L1 expression and immune gene expression and proteomic immune signatures with OR, OS and PFS

2.3.3 To characterize the change in phenotype of TILs, including delineation of effector and regulatory T cells, before and after pembrolizumab treatment

2.3.4 To define T cell receptor (TCR) and B cell receptor (BCR) repertoire profiles that are associated with OR, OS and PFS

2.4 Endpoints

2.4.1 Primary Endpoint

PFS is defined as the time from D1 of treatment to progression or death from any cause. The primary endpoint will be median PFS, but we plan to also report 20 weeks, 1 year and 2 year PFS, each respectively defined as the proportion of patients who are alive and free of progression from disease at the defined time points.

2.4.2 Secondary Endpoints

- Clinician assessed toxicity will be classified and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, version 4.0)
- Patient assessed toxicity will classified based on the Patient-Reported Outcome version of the CTCAE (PRO-CTCAE)
- OR and CR are defined as per RECIST1.1
- OS is defined as the time from D1 of treatment to death from any cause
- Time to locoregional recurrence is defined from D1 of treatment until the first locoregional progression

- Time to distant metastasis is defined as the time from D1 of treatment to progression of disease at a distant site; deaths or other progressions will be censored
- QOL will be evaluated via the FACT-HN

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria to participate in this study:

3.1.1 Be willing and able to provide written informed consent/assent for the trial

3.1.2 Be ≥ 18 years of age on day of signing informed consent

3.1.3 ECOG Performance Status ≤ 1

3.1.4 Histologically or cytologically confirmed stage III-IV (non-metastatic) SCCHN as defined by American Joint Committee on Cancer (AJCC). Nasopharyngeal cancer patients will be excluded. Note that in rare instances, a cancer may be clearly invasive on imaging, but pathology may not be definitive (e.g. in-situ carcinoma); in such cases, the patient will be eligible if the unanimous opinion of the institutional tumor board is that the situation is definitive for invasive SCCHN

3.1.5 Ineligible for high dose cisplatin therapy; the reason for ineligibility must be defined. Acceptable reasons for ineligibility include the following:

- Abnormal renal function (GFR<lower limit of institutional normal (<LLN))
- Abnormal hearing (patient or audiology defined)
- Pre-existing tinnitus
- Neuropathy (bilateral parasthesias or loss of deep tendon reflexes in upper and/or lower extremities)
- Diabetes Mellitus
- Oncologist-certification that patient would not be considered eligible for high dose cisplatin when given as standard of care (for example, due to age or another medical problem); reason should be documented
- Patient refusal for high dose cisplatin

3.1.6 Demonstrate adequate organ function as defined in the table below. All screening labs should be performed within 14 days of treatment initiation.

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 /mcL
Hemoglobin	≥10 g/dL (acceptable to reach this via transfusion)
Renal	
Measured or calculated creatinine clearance (CrCl; GFR can also be used in place of CrCl); see section 11.1 Appendix A for Cockcroft-Gault formula for CrCl)	≥30 mL/min
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN (≤ 3 X ULN if Gilbert's Syndrome) OR
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) 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

3.1.7 No prior curative attempts for this cancer, (i.e., surgery, radiation and/or other)

3.1.8 Female patients 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.

3.1.9 Female patients of childbearing potential must be willing to use adequate method of contraception as outlined in Section 5.1.8 – Contraception, for the course of the study through 120 days after the last dose of study medication**.** Patients of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

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

3.1.10 Male patients must agree to use an adequate method of contraception as outlined in Section 5.1.8 - Contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

3.1.11 As determined by the enrolling physician or protocol designee, ability of the patient to understand and comply with study procedures for the entire length of the study

3.1.12 Consent for the use of any residual material from biopsy (archival tissue) and serial blood draws will be required for enrollment. Patients without adequate tissue for bio-correlates will not be excluded or required to have a repeat biopsy.

3.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria will not be able to participate in this study:

3.2.1 Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.

3.2.2 Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (other than oral contraceptives) or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

3.2.3 Has had a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

3.2.4 Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent. **Note:** If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy. **Note:** Toxicities that specifically define eligibility for this protocol (nephropathy, otopathy, neuropathy, or other as allowed by PI) are exceptions.

3.2.5 Has a known additional malignancy that is metastatic, progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.

3.2.6 Has an active automimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease even if resolved; patients with vitiligo or resolved childhood asthma/atopy would be an

exception to this rule. Patients that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Patients with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study.

3.2.7 Has clinical or radiologic evidence of interstitial lung disease or active, non-infectious pneumonitis.

3.2.8 Has an active infection requiring systemic therapy.

3.2.9 Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating investigator.

3.2.10 Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

3.2.11 Has inadequate home environment or social support to safely complete the trial procedures.

3.2.12 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.

3.2.13 Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways)

3.2.14 Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

3.2.15 Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

3.2.16 Has received a live vaccine within 30 days prior to the first dose of trial treatment.

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

4.0 TREATMENT PLAN

4.1 Study Schema

Pembrolizumab (Pembro) Concomitant with and Post 7 Weeks of Radiation															
Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**	**Week 9**	**Week 10**	**Week 11**	**Week 12**	**Week 13**	**Week 14**	**Week 15**	**Week 16**
IMRT 2Gy/D (M-F)	IMRT 2Gy/D (M-F)	IMRT 2Gy/D (M-F)	IMRT 2Gy/D (M-F)	IMRT 2Gy/D (M-F)	IMRT 2Gy/D (M-F)	IMRT 2Gy/D (M-F)									
Pembro 200mg IV (M)			Pembro 200mg IV (M)			Pembro 200mg IV (M)			Pembro 200mg IV (M)			Pembro 200mg IV (M)			Pembro 200mg IV (M)

M = Monday; M-F = Monday through Friday

Also see section 6.1 for schedule of serial blood draws for biocorrelative studies.

4.2 Radiation Therapy

All patients will receive Intensity Modulated Radiotherapy Treatments (IMRT) as per standard of care (details of which are outlined below). One IMRT plan with 2 to 3 planning target volumes (PTVs) will be created. Dose painting is required. The total dose will be 70 Gy at 2Gy/fx, 35 fractions, Monday to Friday, for 7 weeks.

4.2.1 CT Simulation

CT simulation will be obtained preferably with IV contrast for treatment planning purposes for all patients. The head and neck area will be immobilized with an aquaplast mask. Patients will be positioned in the neck extended position.

4.2.2 Target and Organ at Risk Volumes

4.2.2.1 Gross Tumor Volume (GTV): is defined as all known gross disease determined on the CT simulation scan.

4.2.2.2 High Risk Clinical Target Volumes (CTV-HR) is defined as the GTV plus a non-uniformly expanded 5 to 10 mm to account for high risk areas of microscopic spread. For situations where the primary tumor was removed with the biopsy (e.g. tonsillectomy) and the primary tumor cannot be seen on radiographic imaging the biopsy site will be included in the CTV-HR. A CTV-HR is required for all patients.

4.2.2.3 Intermediate Risk Clinical Target Volume (CTV-IR) is optional except for patients with an unknown primary. For patients with an unknown primary (T0) the ipsilateral oropharynx (base of tongue, tonsil, soft palate) will be included in the CTV-IR volume. Other potential (but not required) indications for contouring a CTV-IR is to include the entirety of nodal level that contains a positive node or to include adjacent nodal levels. For example if there is a node positive in Level 2, the node will be encompassed in the CTV-HR and a CTV-IR may be used to cover the remainder of Level 2 and adjacent Level 3. The purpose in using a CTV-IR is to cover intermediate risk areas of microscopic spread.

4.2.2.4 Standard Risk Clinical Target Volume (CTV-SR) is defined as the elective nodal regions. The consensus guidelines for the node negative and node positive necks published by Gregoire et al. will be used as a guide to define the CTV-SR.[40, 41] For the situation of the unknown primary (i.e. T0), the nasopharynx will be included in the CTV-SR. The following guidelines will be used in delineating the CTV-SR.

- *Node positive hemi-neck* (ipsilateral or contralateral to the primary site) [40]: The following elective nodal regions should be included in the CTV-SR: Levels Ib-V. The retropharyngeal region should also be included in oropharyngeal and hypopharyngeal primary tumors. The cranial extent to the base of skull of Level II and retropharyngeal nodes should be electively irradiated for oropharyngeal and hypopharyngeal primary tumors.
- *Ipsilateral node negative hemi-neck [41]* The following elective nodal regions should be included in the CTV-SR: Levels II –IV. The retropharyngeal region should also be included in oropharyngeal and hypopharyngeal primary tumors. The cranial extent to the base of skull of Level II and retropharyngeal nodes should be electively irradiated for oropharyngeal and hypopharyngeal primary tumors.
- *Contralateral node negative hemi-neck[41, 42]:* The contralateral parotid may be spared by omitting irradiation of the cranial portion of Level II and retropharyngeal region, defined as the Level II, retropharyngeal region above the transverse process of the C1 vertebrae and/or where the posterior belly of the digastric muscle crosses over the jugular vein.
- *Omission of Contralateral neck negative hemi-neck irradiation*: Contralateral neck irradiation may be completely omitted for well lateralized tonsil cancers, defined as having no invasion of the base of tongue, and minimal invasion of the soft palate (i.e. > 1 cm from the uvula). Bilateral neck radiation is required for larynx and hypopharyngeal primary tumors. The contralateral node negative neck may be omitted in a well lateralized T1-T2 oral cavity cancer (i.e. oral tongue, alveolar ridge, buccal cavity).
- *Unknown Primary:* The above elective nodal irradiation guidelines will be used. Furthermore the nasopharynx will be included in the CTV-SR.

4.2.2.5 Planning Target Volumes (PTV): To account for daily setup errors, the CTV's will be expanded uniformly by 3 mm to create a High Risk Planning Target Volume (PTV-HR), Intermediate Risk Planning Target Volume (PTV-IR), and

a Standard Risk Planning Target Volume (PTV-SR). The PTV-IR is optional except for unknown primary tumors (see above section 4.2.2.3)

4.2.2.6 Organs at Risk (OAR): The following normal tissues will be segmented on CT simulation scan: spinal cord, brainstem, parotids, cochleae, and larynx.

4.2.2.7 Planning Risk Volumes (PRV): OAR(s) will be uniformly expanded 3mm to create individual Planning Risk Volumes (PRV)

4.2.3 Dose Specification

Dose painting IMRT will be used and all doses will be specified to the PTV. The PTV-HR, PTV-IR, and PTV-SR will be treated to the following respective total doses: 70 Gy, 63 Gy, and 54 Gy. The dose per fraction to the PTV-HR, PTV-IR, and PTV-SR will be 2 Gy per day, 1.8 Gy per day, and 1.54 Gy respectively. Thus the total number of fractions will be 35. All fields will be treated once a day Monday through Friday.

4.2.4 IMRT Treatment Planning

PTV's and PRV will be included in the IMRT optimization. Seven to nine equidistant fields will be placed around the PTV. None of the beams will directly oppose one another. Tomotherapy® and other arc-based IMRT technologies (VMAT®, RapidArc®) are allowed. Dose objectives will be chosen for the IMRT optimization based on previous institutional experience. Dose painting (i.e. simultaneous integrated boost) will be used to create one IMRT plan. The PTV-SR contours will encompass the PTV-IR and PTV-HR contours. IMRT to treat the entire neck is preferred, however a matched low anterior neck field technique may be used only if it does not result in significant dose heterogeneity for the PTV-HR.

4.2.5 Regimen

Radiation continues for 35 consecutive weekdays. Patient will receive 2 Gy daily fractions of radiotherapy without a break except for weekends and holidays.

4.2.6 Dose Constraints

- PTV-HR and PTV-SR
  - 100% of the prescription should cover 95% of the PTV
  - No more than 20% of the PTV should receive ≥ 110% of the prescribed dose.
  - No more than 1% of the PTV should receive ≤ 93% of the prescribed dose
- Non-target Tissue
  - No more than 1% of the tissue outside the PTV should receive ≥ 110% of the prescribed dose
- PRV
  - Spinal Cord: 0.1cc ≤ 50 Gy
  - Brainstem: 0.1cc ≤ 54 Gy
  - Parotid: Mean dose < 26 Gy and/or 50% < 30 Gy
  - Cochlea: Mean dose < 45 Gy
  - Larynx: Mean dose < 41 Gy and/or 60 Gy to < 20%

PTV coverage should not be compromised to meet the dose constraints of the parotid, cochlea, or larynx. Sparing of these structures is left at the discretion of the treating radiation oncologists. The dose constraints for the spinal cord and brainstem must be satisfied. This may be done at the cost of altering the PTV.

4.2.7 Treatment Verification

Weekly orthogonal films or cone beam CT's should be performed to verify patient setup (at least)

4.2.8 Rests and Interruptions

For acute radiation toxicities, treatment breaks should be kept to a minimum. An effort will be made to complete the radiotherapy on schedule without significant treatment breaks, as prolongation of treatment is known to contribute to treatment failure. The need for radiotherapy breaks due to severe acute toxicity will be determined by the treating radiation oncologist. If radiation therapy is held, pembrolizumab therapy may continue as per the discretion of the investigator, and based on the nature of the toxicity.

The specific reason(s) for any treatment interruption must be recorded in the treatment chart and the electronic case report form (e-CRF). Treatment interruptions exceeding fourteen (14) days for reasons other than protocol-mandated interruptions for adverse events will be considered a major protocol deviation. No modifications in dose will be made for interruptions in therapy.

4.2.9 Patient Monitoring During Treatment

During radiation therapy, all patients will be seen by a healthcare provider for radiation therapy management visits per institutional standard of care, typically at least weekly.

4.2.10 Supportive care during radiation therapy

Routine management of toxicities during radiation therapy is allowed. Interventions may include, but are not limited to, the following:

Toxicity	Management
Skin reactions:	Topical agents such as Aquaphor® or Biofene®
Dehydration:	IV fluids as needed

4.3 Pembrolizumab

4.3.1 Dosing Administration

Starting on the first day of radiotherapy, patients will be treated with pembrolizumab 200mg IV every 3 weeks for 6 doses.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution. This manual is provided as a document separate from the protocol.

NOTE: Subjects should be assessed for possible Events of Clinical Interest (ECI; see the document provided separate from this protocol) 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 no other cause is found, then it is assumed to be immune-related.

4.3.2 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. Refer to the table below for infusion reaction treatment guidelines associated with administration of pembrolizumab.

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Stop Infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., 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.	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: 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.		

4.3.3 Other Dose Modifications

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 below. Also see section 4.3.4 for supportive care guidelines of drug-related events. See Section, including use of corticosteroids.

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 dose of pembrolizumab is delayed, then the subsequent dose should be administered 3 weeks later. When pembrolizumab is delayed or held, radiation may and should continue if clinically appropriate. Patients may receive up to 6 total doses of pembrolizumab, even if doses are delayed to the point that they do not overlap with radiation. If radiation therapy is held, pembrolizumab therapy may continue as per the discretion of the investigator, and based on the nature of the toxicity.

Hematological Toxicity Dose Delays or Discontinuation for Pembrolizumab

Toxicity	Hold Treatment For Grade	Timing for Restarting Pembrolizumab*	Discontinue Subject**
Autoimmune hemolytic anemia, aplastic anemia, disseminated intravascular coagulation, Hemolytic Uremic Syndrome (HUS-Idiopathic or immune), Thrombocytopenia Purpura (ITP), Thrombotic Thrombocytopenic Purpura (TTP) or Any Grade 4 anemia regardless of underlying mechanism	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue**	Permanently discontinue**

**Whenever pembrolizumab is permanently discontinued, patient should still be followed-up per protocol.

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	old pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients are clinically and metabolically stable
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism	2	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

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

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

[2b] 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; Refer to Table 2 – Infusion Treatment Guidelines for further management details.

[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

4.3.4 Rescue Medications & Supportive Care

Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. 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 does not need to follow the treatment guidance as outlined below. Refer to Section 4.3.3 for dose modifications.

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

Hematologic (see table in Section 4.3.3 for what is considered hematologic ECI)

All attempts should be made to rule out other causes such as metastases, sepsis and/or infection. Relevant diagnostic studies such as peripheral blood smear, reticulocyte count, LDH, haptoglobin, bone marrow biopsy or Coomb's test, etc., should be considered to confirm the diagnosis.

For Grade 2 events:

- Hold pembrolizumab
- Prednisone 1-2 mg/kg daily may be indicated
- Consider Hematology consultation
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3 events:

- Hematology consultation
- Hold pembrolizumab
- Discontinuation should be considered at discretion of investigator
- Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

- Hematology consultation
- Discontinue pembrolizumab
- Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate

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,** administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Type 1 diabetes mellitus (TIDM) (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 TIDM 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.

Infusion Reaction
See section 4.3.2

4.4 Concomitant Medications/ Vaccinations (allowed & prohibited)

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

4.4.1 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.

4.4.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase

- Anti-cancer systemic chemotherapy or 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, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
- Radiation therapy

- Note: Radiation therapy to a symptomatic solitary lesion may be allowed at the investigator's discretion.

Subjects who are removed from study treatment per above guidelines should be treated per standard of care.

4.5 Duration of Therapy

In the absence of treatment delays due to AEs, treatment may continue until the end of study-defined treatment or until:

- Inter-current illness that prevents further administration of treatment
- Unacceptable toxicity
- Pregnancy
- Patient decides to withdraw from study treatment, **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.6 Duration of Follow-Up

Patients will be followed for up to 5 years after removal from study treatment or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. After two years of follow-up as described in the time and events table, subsequent follow-up will be per standard of care and the study will follow only for progression and for survival for up to 3 additional years, for a total of 5 years of follow-up after completion of treatment.

4.7 Removal of Patients from Protocol Therapy

Patients will be removed from protocol therapy and the PI notified when any of the criteria listed in section 4.5 apply. The reason for discontinuation of protocol therapy will be documented on the eCRF.

In case a patient decides to prematurely discontinue protocol therapy ("refuses treatment"), the patient should be asked if she or he may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.

4.8 Study Withdrawal

If a patient decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. The investigator should contact the patient or a responsible relative by telephone or through a personal visit to establish as completely as possible the reason for the study withdrawal. A complete final evaluation at the time of the patient's study withdrawal should be made with an explanation of why the patient is withdrawing from the study. If the reason for removal of a patient from the study is an adverse event, the principal specific event will be recorded on the eCRF. Excessive patient withdrawals from protocol

therapy or from the study can render the study un-interpretable; therefore, unnecessary withdrawal of patients should be avoided.

5.0 DRUG INFORMATION

5.1 Pembrolizumab

5.1.1 Description

Clinical Supplies will be provided by Merck as summarized in the table below.

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

5.1.2 Supplier/How Supplied

Pembrolizumab will be provided at no cost to the study patient by Merck, the manufacturer of the drug. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

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.

5.1.3 Handling and Dispensing

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.

5.1.4 Storage and Stability

As per the pharmacy manual, which will be provided as a document separate from the protocol.

5.1.5 Return and Retention

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

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per UNC IDS drug destruction 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.

5.1.6 Adverse Events Associated with Pembrolizumab

The most common adverse reactions (reported in ≥20% of patients in clinical trials of pembrolizumab) included fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, and diarrhea. The following warnings are associated with the use of pembrolizumab:

Immune-Mediated Pneumonitis
Pneumonitis occurred in ~3% of melanoma patients treated in clinical trials of pembrolizumab. The median time to development of pneumonitis was 5 months with a median duration of 4.9 months. The one patient with Grade 3 pneumonitis required initial treatment with high-dose systemic corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) followed by a corticosteroid taper. Pneumonitis completely resolved in seven of the nine patients with Grade 2-3 pneumonitis.

Immune-Mediated Colitis
Colitis (including microscopic colitis) occurred 1% of melanoma patients treated in clinical trials of pembrolizumab. The median time to onset of was 6.5 months with a median duration of 2.6 months. All three patients with Grade 2 or 3 colitis were treated with high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day).

Immune-Mediated Hepatitis
Hepatitis (including autoimmune hepatitis) occurred in 0.5% of melanoma patients treated in clinical trials of pembrolizumab. The time to onset was 22 days for the case of Grade 4 hepatitis which lasted 1.1 months. The patient with Grade 4 hepatitis permanently discontinued pembrolizumab and was treated with high-dose (greater than or equal to 40 mg prednisone or equivalent per day) systemic corticosteroids followed by a corticosteroid taper. Both patients with hepatitis experienced complete resolution of the event.

Immune-Mediated Hypophysitis
Hypophysitis occurred in 0.5% of melanoma patients treated in clinical trials of pembrolizumab. The time to onset was 1.7 months for the patient with Grade 4 hypophysitis and 1.3 months for the patient with Grade 2 hypophysitis. Both patients were treated with high-dose (greater than or equal to 40 mg prednisone or

equivalent per day) corticosteroids followed by a corticosteroid taper and remained on a physiologic replacement dose.

Renal Failure and Immune-Mediated Nephritis
Nephritis occurred in 3 (0.7%) patients of melanoma patients treated in clinical trials of pembrolizumab, consisting of one case of Grade 2 autoimmune nephritis (0.2%) and two cases of interstitial nephritis with renal failure (0.5%), one Grade 3 and one Grade 4. The time to onset of autoimmune nephritis was 11.6 months after the first dose of pembrolizumab (5 months after the last dose) and lasted 3.2 months; this patient did not have a biopsy. Acute interstitial nephritis was confirmed by renal biopsy in two patients with Grades 3-4 renal failure. All three patients fully recovered renal function with treatment with high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) followed by a corticosteroid taper.

Immune-Mediated Hyperthyroidism
Hyperthyroidism occurred in 5 (1.2%) of 411 melanoma patients treated in clinical trials of pembrolizumab. The median time to onset was 1.5 months and the median duration was 2.8 months (range 0.9 to 6.1). One of two patients with Grade 2 and the one patient with Grade 3 hyperthyroidism required initial treatment with high-dose corticosteroids (greater than or equal to 40 mg prednisone or equivalent per day) followed by a corticosteroid taper. One patient (0.2%) required permanent discontinuation of pembrolizumab due to hyperthyroidism. All five patients with hyperthyroidism experienced complete resolution of the event.

Immune-Mediated Hypothyroidism
Hypothyroidism occurred in 34 (8.3%) of 411 melanoma patients treated in clinical trials of pembrolizumab. The median time to onset of hypothyroidism was 3.5 months. All but two of the patients with hypothyroidism were treated with long-term thyroidhormone replacement therapy. The other two patients only required short-term thyroid hormone replacement therapy. No patient received corticosteroids or discontinued pembrolizumab for management of hypothyroidism. Thyroid disorders can occur at any time during treatment.

Other Immune-Mediated Adverse Reactions
Other clinically important immune-mediated adverse reactions can occur. The following clinically significant, immune-mediated adverse reactions occurred in less than 1% of patients treated with pembrolizumab, including exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, partial seizures arising in a patient with inflammatory foci in brain parenchyma, and adrenal insufficiency.

Across clinical studies with pembrolizumab in approximately 2000 patients, the following additional clinically significant, immune-mediated adverse reactions

were reported in less than 1% of patients: myasthenic syndrome, optic neuritis, and rhabdomyolysis.

Embryofetal Toxicity
Based on its mechanism of action, pembrolizumab may cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PD-L1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue.

5.1.7 Contraindications

There are no reported contraindications associated with the use of pembrolizumab.

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.

5.1.8 Contraception

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

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

Female subjects will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence† from heterosexual activity;

OR

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

Acceptable methods of contraception are‡:
Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection.

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.1.9 Use in Pregnancy

If a patient inadvertently becomes pregnant while on treatment with pembrolizumab, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the

pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the UNCCN Project Manager who will report the event to Merck without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the UNCCN Project Manager and Merck as described above.

If a male patient impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the UNCCN Project Manager and to Merck and followed as described above and in Section 7.3.3.

5.1.10 Use in Nursing Women

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

5.1.11 Overdose

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 UNCCN Project Manager who will report the event within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220) (see section 7.3.3).

6.0 EVALUATIONS AND ASSESSMENTS

6.1 Time and Events Table

Procedure	Screening[1]	D1 cycle 1[2]	D1 cycle 2[2]	D1 cycle 3[2]	D1 cycle 4[2]	D1 cycle 5[2]	D1 cycle 6[2]	D1 Week 20[3,4]	Long-Term Follow-up[5]
Informed Consent	X								
Dental exam	X[1]								
Charleson Comorbidity Index (CCMI)	X								
Physical Exam & Medical History	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]
ECOG Performance Status	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X
CBC w/differential	X	X	X	X	X	X	X	X	X
Serum chemistries[7] and LFTs[8]	X	X	X	X	X	X	X	X	X
Urine or serum pregnancy	X[9]								
Coagulation, urinalysis[10]	X[10]			X[10]				X[10]	
Thyroid Panel	X[11]			X[11]				X[11]	X[11]
Uric acid	X								
Radiographic tumor evaluation	X[1]							X[4]	X[5]
Clinician toxicity assessment[12]	X	X	X	X	X	X	X	X	X
PRO-CTCAE and Quality of Life[13]		X[13]			X[13]			X[13]	
Pembrolizumab 200mg IV		X	X	X	X	X	X		
Radiation		M-F daily IMRT x 7 weeks							
Concomitant Med Review	X	X	X	X	X	X	X	X	
Progression/Survival									X
Request archival tissue	X[1,14]								
Blood draw for correlates (required)		X[15]						X[15]	X[15]
Respiratory signs/symptoms	X[16]	Check respiratory signs/symptoms[16]							

Key to Time and Events Table Footnotes

[1]Unless otherwise noted, screening evaluations to take place within 2 weeks of day 1 (D1) of study treatment. Archival tissue, if available, may be obtained at any point during conduct of the study. Dental exam must take place within 6 weeks of D1 of treatment. Baseline imaging will require neck CT or MRI (either with contrast) as well as chest imaging (either chest CT (recommended) or chest x-ray). If PET-CT (or PET-MRI) is clinically indicated additional chest and neck CT will not be necessary. Baseline imaging must be acquired within 4 weeks of the start of treatment. Dental evaluation is as required per standard of care evaluation (eg, a patient with clearly healthy dentition who would not be formally evaluated by a dentist as part of standard of care is not required to do so as part of this study).

[2]Each cycle (total of 6 cycles) is defined by pembrolizumab infusion (every 3 weeks unless delayed, so lasting ~18 weeks), and the duration of XRT is typically 7 weeks; a window of +/-3 days will apply to all study visits. Laboratory evaluations on day 1 of cycle 1 need be repeated only if >7 days have elapsed between screening laboratory tests and day 1. Typical radiation schema is shown here, but radiation is to be IMRT given per protocol.

[3] 30 days (+/- 4 days) post last dose of pembrolizumab, whether treatment was discontinued because all doses were completed, or due to toxicity, progression etc., patients will be evaluated for 30 day post pembrolizumab safety. In patients who complete all doses on time, this visit should occur at week 20. Patients who are still experiencing a treatment-related ≥ Grade 2 adverse event will be contacted every 2 weeks until the event is resolved to Grade 0 or 1, determined to be irreversible by the investigator, or until the patient begins an alternate form of treatment.

[4]At week 20 of the study, (~12 weeks (+/- 7 days) after the last dose of radiation), a PET scan is required. If PET was done at baseline, remain consistent with the type of PET scan (either PET-CT or PET-MRI). If a PET scan is refused by insurance, a neck CT or MRI (consistent with the test ordered at baseline whether associated with PET or not) will be acceptable.

[5] Serious adverse events (SAEs) or any grade of Events of Clinical Interest (see section 7.3 and the ECI Guidance Document that is provided as a document separate from this protocol) that occur within 90 days of the end of pembrolizumab (or prior to start of new anti-cancer therapy) must be recorded. If all cycles occur on schedule, this should correspond to approximately week 28. Long-term follow-up visits will start at this week 28 visit, and then take place every 3 months (+/- 30 days) thereafter for one year, then every 6 months (+/- 45 days) for a year. Imaging will consist of a neck CT or MRI (consistent with the test ordered at baseline) during each of these visits (PET is not required). Indeterminate pulmonary nodules should be followed per institutional standard of care. Screening chest CT is recommended at least annually for patients with a smoking history. After two years, follow up is per institutional care and documentation for study purposes will be limited to first subsequent anti-cancer treatment, and PFS and OS only for a maximum of five years.

[6]Complete history at baseline only (including smoking history), thereafter focused history on symptoms/toxicity.

[7]Serum chemistries and electrolytes to include sodium, potassium, phosphorus, chloride, bicarbonate, BUN, serum creatinine, glucose, calcium, magnesium, albumin

[8]LFTs (liver function tests) include total bilirubin, alkaline phosphatase, AST, ALT

[9]Urine or serum β-HCG to be done within 72 hours of day 1 of treatment in women of childbearing potential; if the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required**.**

[10]Coagulation includes PT/INR and PTT; Urinalysis includes blood, glucose, protein, specific gravity, and microscopic exam if abnormal results are noted

[11]Thyroid panel includes TSH, T3 and free T4. If consistent with institutional standard of care, it is acceptable to obtain TSH **alone** and only obtain T3 and free T4 if clinically useful.

[12]Via NCI CTCAEv4.0

[13]See section 6.5 for tools and schedule of these assessments during follow-up; Quality of life will be measured by the FACT-HN (see Section11.2, Appendix B).

[14]Tissue from diagnostic biopsy, when available, will be requested for correlative studies. Further details to be provided in a laboratory manual.

[15]Blood draw (see section 6.6.2; 3x 8mLs whole blood in ACD tubes and one serum separator tube (gel barrier) required at each scheduled draw) will be to evaluate for clonally restricted circulating B and T cells and for proteomics. The draws will be on C1 (pre-pembrolizumab), 4 weeks following the last dose of pembrolizumab, and at the second long-term follow-up visit (approximately week 40 from start of treatment)

[16]Perform baseline assessment and check for history of pneumonitis, monitor for respiratory signs/symptoms while patients are on pembrolizumab and manage toxicity for pneumonitis as outlined in section 4.3.4

a) If applicable: ongoing patients are to be evaluated for active pneumonitis. Patients with a history of pneumonitis should be re-consented for this trial to consider if they should discontinue pembrolizumab or continue treatment based on the risk of fatal pneumonitis related to pembrolizumab therapy.

6.2 Pre-Study Assessments

Clinical evaluation: complete history, CCMI (see section 11.3, Appendix C), physical examination to include height (baseline only) and weight, dental exam; ECOG performance status.
Laboratory studies:

- **Pregnancy Test**: A urine or serum pregnancy test (β-HCG) is required for all women of childbearing potential at screening within 72 hours prior to the first dose of treatment under this protocol. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
- **CBC with differential**
- **Serum Chemistries:** These include the following parameters: sodium, potassium, phosphorus, chloride, bicarbonate, BUN, serum creatinine (calculate creatinine clearance via Cockcroft-Gault, see section 11.1 Appendix A), glucose, calcium, magnesium, albumin
- **LFTs:** These include total bilirubin (direct and indirect), alkaline phosphatase, AST (SGOT), ALT (SGPT)
- **Uric acid**
- **Urinalysis:** includes blood, glucose, protein, specific gravity, and microscopic exam if abnormal results are noted
- **Coagulation Studies:** PT/INR and PTT
- **Thyroid Panel:** TSH, T3, free T4; if consistent with institutional standard of care, it is acceptable to obtain TSH alone and only obtain T3 and free T4 if clinically useful.

Check respiratory history (signs/symptoms):
Archival tissue**:** request access to archival tissue to support correlative studies (see section 6.6); consent for the use of any residual material from biopsy will be required for enrollment. Patients without adequate tissue for bio correlates will not be excluded or required to have a repeat biopsy.
Concomitant Medications**:** Review (see section 4.4)
Toxicity Assessment**:** per NCI CTCAEv4
Tumor imaging**:** Baseline imaging will require neck CT or MRI (either with contrast) as well as chest imaging (either chest CT (recommended) or chest x-ray). If PET-CT (or PET-MRI) is clinically indicated additional chest and neck CT will not be necessary

6.3 Treatment Assessments

6.3.1 D1 Cycle 1

Clinical evaluation: focused history on symptoms/toxicity, physical examination including weight and ECOG performance status.
Laboratory studies:

- **CBC with differential**
- **Serum Chemistries:** These include sodium, potassium, phosphorus, chloride, bicarbonate, BUN, serum creatinine, glucose, calcium, magnesium, albumin

- **LFTs:** These include total bilirubin (direct and indirect), alkaline phosphatase, AST (SGOT), ALT (SGPT)

Check Respiratory signs/ Symptoms:
Concomitant Medications: Review
Toxicity: Per both NCI CTCAEv4 and PRO-CTCAE (see section 6.5)
QOL: FACT-HN (see section 11.2, Appendix B)
Blood Draws for Correlatives: see section 6.6.2; 3x 8mLs whole blood in ACD tubes and a serum separator tube (gel barrier) required at each scheduled draw (Required)

6.3.2 D1 Cycle 2, 5 and 6

Clinical evaluation: focused history on symptoms/toxicity, physical examination including weight and ECOG performance status.
Laboratory studies:

- **CBC with differential**
- **Serum Chemistries:** These include sodium, potassium, phosphorus, chloride, bicarbonate, BUN, serum creatinine, glucose, calcium, magnesium, albumin
- **LFTs:** These include total bilirubin (direct and indirect), alkaline phosphatase AST (SGOT), ALT (SGPT)

Check Respiratory signs/ Symptoms:
Concomitant Medications: Review
Toxicity: Per NCI CTCAEv4

6.3.3 D1 Cycle 3

Clinical evaluation: focused history on symptoms/toxicity, physical examination including weight and ECOG performance status.
Laboratory studies:

- **CBC with differential**
- **Serum Chemistries:** These include sodium, potassium, phosphorus, chloride, bicarbonate, BUN, serum creatinine, glucose, calcium, magnesium, albumin
- **LFTs:** These include total bilirubin (direct and indirect), alkaline phosphatase AST (SGOT), ALT (SGPT)
- **Urinalysis:** includes blood, glucose, protein, specific gravity, and microscopic exam if abnormal results are noted
- **Coagulation Studies:** PT/INR and PTT
- **Thyroid Panel:** TSH, T3, free T4; if consistent with institutional standard of care, it is acceptable to obtain TSH alone and only obtain T3 and free T4 if clinically useful.

Check Respiratory signs/ Symptoms:
Concomitant Medications: Review
Toxicity: Per NCI CTCAEv4

6.3.4 D1 Cycle 4

Clinical evaluation: focused history on symptoms/toxicity, physical examination including weight and ECOG performance status.
Laboratory studies:

- **CBC with differential**
- **Serum Chemistries:** These include sodium, potassium, phosphorus, chloride, bicarbonate, BUN, serum creatinine, glucose, calcium, magnesium, albumin
- **LFTs:** These include total bilirubin (direct and indirect), alkaline phosphatase AST (SGOT), ALT (SGPT)

Check Respiratory signs/ Symptoms:
Concomitant Medications: Review
Toxicity: Per both NCI CTCAEv4 and PRO-CTCAE (see section 6.5)
QOL: FACT-HN (see section 6.5)

6.4 Follow-Up

6.4.1 D1 Week 20

Clinical evaluation: focused history on symptoms/toxicity, physical examination including weight and ECOG performance status.
Laboratory studies:

- **CBC with differential**
- **Serum Chemistries:** These include sodium, potassium, phosphorus, chloride, bicarbonate, BUN, serum creatinine, glucose, calcium, magnesium, albumin
- **LFTs:** These include total bilirubin (direct and indirect), alkaline phosphatase AST (SGOT), ALT (SGPT)
- **Urinalysis:** includes blood, glucose, protein, specific gravity, and microscopic exam if abnormal results are noted
- **Coagulation Studies:** PT/INR and PTT
- **Thyroid Panel:** TSH, T3, free T4; if consistent with institutional standard of care, it is acceptable to obtain TSH alone and only obtain T3 and free T4 if clinically useful.

Check Respiratory signs/ Symptoms:
Concomitant Medications: Review
Toxicity: Per both NCI CTCAEv4 and PRO-CTCAE (see section 6.5)
QOL: FACT-HN (see section 11.2, Appendix B)
Blood Draws for Correlatives: see section 6.6.2; 3x 8mLs whole blood in ACD tubes and serum separator (gel barrier) required at each scheduled draw (Required)
Tumor Imaging: At this visit, a PET scan is required. If PET was done at baseline, remain consistent with the type of PET scan (either PET-CT or PET-MRI). If a PET scan is refused by insurance, a neck CT or MRI (consistent with the test ordered at baseline whether associated with PET or not) will be acceptable.

6.4.2 Long-Term Follow-Up

Long-term follow-up visits will start at week 28, and then take place every 3 months (+/- 30 days) thereafter for one year, then every 6 months (+/- 45 days) for a year. After two years, follow-up is per institutional care and documentation for study purposes will be limited to first subsequent anti-cancer treatment, PFS and OS only for a maximum of five years.

Clinical evaluation: Per institutional standard of care.
Toxicity evaluation: Serious adverse events (SAEs) or any grade of Events of Clinical Interest (see section 7.3 and the ECI Guidance Document that is provided as a document separate from this protocol) that occur within 90 days of the end of pembrolizumab (or prior to start of new anti-cancer therapy) must be recorded. If all cycles occur on schedule, this should correspond to approximately week 28.
Laboratory studies:

- **CBC with differential**
- **Serum Chemistries:** These include sodium, potassium, phosphorus, chloride, bicarbonate, BUN, serum creatinine, glucose, calcium, magnesium, albumin
- **LFTs:** These include total bilirubin (direct and indirect), alkaline phosphatase AST (SGOT), ALT (SGPT)
- **Thyroid Panel:** TSH, T3, free T4; if consistent with institutional standard of care, it is acceptable to obtain TSH alone and only obtain T3 and free T4 if clinically useful.

Tumor imaging: For the first 2 years of follow-up, imaging will consist of a neck CT or MRI (consistent with the test ordered at baseline) during each of these visits (PET is not required). Indeterminate pulmonary nodules should be followed per institutional standard of care. Screening chest CT is recommended at least annually for patients with a smoking history.
Blood Draws for Correlatives: see section 6.6.2; 3x 8mLs whole blood in ACD tubes and a serum separator tube (gel barrier) (Required) at the second long-term follow-up visit (~week 40 from start of treatment)

6.5 Patient Reported Outcomes version of the CTCAE

A subset of items pertinent to H&N cancer will be drawn from the PRO-CTCAE system. These items will be used to evaluate the presence and/or severity of range of symptoms, as well as the degree to which symptom/toxicity interferes with usual function. These measures are:

- Atttention/Memory: Concentration, memory
- Cutaneous: Rash, hair loss
- Pain: General pain, headache
- GI: Taste changes, decreased appetite, nausea, vomiting, diarrhea
- Sleep/wake: Insomnia, fatigue
- Respiratory: Shortness of breath, cough, wheezing
- Neurologic: numbness and tingling, dizziness
- Mood: anxious, discouraged, sad

- Misc: Nosebleed
- Visual/perceptual: Ringing ear
- Oral: dry mouth, difficulty swallowing, mouth/throat sores, cehliosis, voice quality changes, hoarseness

6.6 Correlative Studies Procedures

These are described in more detail in the laboratory manual.

6.6.1 Archival Tissue

Archival tumor tissue (paraffin-embedded blocks/slides) from the patient's original diagnostic biopsy will be requested and collected from all enrolled patients. See accompanying laboratory manual for additional details.

6.6.2 Blood samples

Patients will have a three ACD tubes (whole blood, 3 x 8mL) and a serum separator tube (gel barrier) collected at the times as noted in the Time and Event table. Sample collection, storage, and shipment instructions for serum samples will be provided in the Laboratory Manual.

6.7 Assessment of Safety

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed periodically for the development of any toxicity according to the Time and Events table (section 6.0). Toxicity will be assessed according to the NCI CTCAE v4. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment. Patient reported outcomes will be assessed via the PRO-CTCAE, see section 6.5.

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 ECI of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see the separate ECI guidance document (provided as a document separate from this protocol) regarding the identification, evaluation and management of potential irAEs.

Please refer to section 7.0 for detailed information regarding the assessment and recording of AEs.

6.8 Assessment of Efficacy

Patients who have received at least 1 dose of pembrolizumab will be evaluable for assessment of response and progression. Patients whose cancer growth is documented by physical examination without imaging confirmation will count as progression. Patients who drop out of the study for any reason (ex. toxicity of treatment, decide to withdraw) will still be followed for PFS and OS.

6.8.1 Assessment of Disease-Tumor Measurement Based on RECIST 1.1

Measurable disease will be defined as the presence of at least one measurable lesion that can be accurately measured in at least one dimension with the longest diameter a minimum size of:

- ≥10mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest x-ray.

For malignant lymph nodes to be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5mm). At baseline and in follow-up, only the short axis will be measured and followed.

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions, will be considered non-measurable. Lesions considered truly non-measurable include:leptomeningeal disease; ascites; pleural/pericardial effusion; inflammatory breast disease; lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesions is recommended.

6.8.2 Baseline Documentation of Target and Non-Target Lesions

All measurable lesions up to a maximum of 5 lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longer diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent", or in rare cases "unequivocal progression".

6.8.3 Evaluation of Target Lesions using RECIST 1.1 Criteria

Complete response (CR)−Disappearance of all target lesions. Any pathological lymph node (LN) (whether target or non-target) must have decreased in short axis to <10mm.

Partial response (PR)−At least a 30% decrease in the sum of the LD of the target lesions taking as reference the baseline sum LD.

Progressive Disease (PD)−At least a 20% increase in the sum of the LD of the target lesions taking as reference the smallest sum LD recorded since the treatment started including baseline if that is the smallest on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. The appearance of one or more new lesions also constitutes PD.

Stable disease (SD)−Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD since the treatment started.

6.8.4 Evaluation of Non-Target Lesions using RECIST 1.1 Criteria

Complete response (CR)−Disappearance of all non-target lesions and normalization of tumor marker levels. All LN must be non-pathological in size (<10mm short axis).

Non-complete response (non-CR)/non-progression (non-PD)−Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.

Progressive disease (PD)−Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

7.0 ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a drug) in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the investigator to the study therapy.

All adverse events that occur after the consent form is signed but before treatment must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.1.4. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

7.1.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the drug is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study drug exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than once occurrence from one or multiple studies would be needed before the sponsor could determine that there is *reasonable possibility* that the drug caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the drug treatment group than in a concurrent or historical control group.

7.1.3 Unexpected AE or SAR

An AE or SAR is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., Investigator's Brochure (IB) for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious AE or SAR

An AE or SAR is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed

in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

Pregnancy that occurs during the study must also be reported as an SAE.

- Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
    - Is a new cancer (that is not a condition of the study);
    - Is associated with an overdose.

For the time period beginning when the consent form is signed until treatment, 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 must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

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 following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck Global Safety.

All subjects with serious adverse events must be followed up for outcome.
SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220

7.2 Documentation of non-serious AEs or SARs

For non-serious AEs or SARs, documentation must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

Collected information should be recorded in the Case Report Forms (CRF) for that patient. Please include a description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least monthly.

7.3 SAEs or Serious SARs and Events of Clinical Interest

7.3.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g. SAEs related to invasive procedures such as biopsies, medication washout.

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin from day 1 of study treatment and continue through the 90 day follow-up period after treatment is discontinued (or to the initiation of new anti-cancer treatment, whichever is earliest).

7.3.2 Documentation and Notification

SAEs or Serious SARs must be recorded in the SAE console within Oncore™ for that patient within 24 hours of learning of its occurrence. Additionally, the NCCN Project Manager must also be notified via email of all SAEs within 24 hours of learning of its occurrence.

7.3.3 Reporting

IRB Reporting Requirements:

UNC**:**

- UNC will submit an aggregated list of all SAEs to the UNC IRB annually at the time of study renewal according to the UNC IRB policies and procedures.
- The UNC-IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting system (see section 9.5.3) within 7 days of the Investigator becoming aware of the problem.

Affiliate sites:

- For affiliate sites using a local IRB of record, please submit adverse events per local IRB policy.

For affiliate sites relying on the UNC-IRB, an aggregated list of all SAEs will be submitted to the UNC IRB annually at the time of study renewal according to the UNC IRB policies and procedures. In addition, any SAEs that qualify as an Unanticipated Problem will be entered into Oncore and reported to the UNC IRB by the UNCCN Project Manager using the IRB's web-based reporting system (see section 9.5.3) within 7 days of the Investigator becoming aware of the problem.

Pregnancy

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. Pregnancies and lactations that occur after the consent form is signed but before treatment must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

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, as a serious adverse event. The patient is to be discontinued immediately from any protocol directed therapy. 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 adverse 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 UNCCN Project Manager who will report the event within 2 days to the manufacturer (Merck; see below).

The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the UNCCN Project Manager within 24 hours via facsimile to 919-966-4300. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

FDA Expedited Reporting requirements:

If an investigator deems that an event is both a serious SAR AND unexpected, it must also (in addition to Oncore) be recorded on the MedWatch Form 3500A as per 21 CFR 312.32. The MedWatch form should be faxed to the UNCCN Project Manager at 919-966-4300 (or emailed, with address provided at the Start up Meeting (SIM)) along with supporting documentation defining the event and causality. The UNCCN Project Manager will send report to Merck. The MedWatch 3500a form can be accessed at:

http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

(Please be sure and access form 3500a, and not form 3500). UNC, as the Sponsor of the study, will make the final determination regarding FDA submission.

Once the UNC Principal Investigator determines an event is a serious SAR AND unexpected, the MedWatch 3500A form will be submitted to the FDA.

The UNCCN Project Manager will also be responsible for informing each Affiliate site of all serious and unexpected SARs reported to the FDA via fax as soon as possible.

Merck Reporting Requirements:
Any SAE, or follow up to a SAE, 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 UNCCN Project Manager who will report the event within 2 working days to Merck Global Safety. All subjects with serious adverse events must be followed up for outcome.

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 UNCCN Project Manager who will report the event to Merck.

SAE reports and any other relevant safety information are to be forwarded to the UNCCN Project Manager via facsimile at 919-966-4300, or scanned and emailed to UNCCN Project Manager (address to be provided at the SIM) who will then fax to the Merck Global Safety facsimile number: +1-215-993-1220.

All 15-Day Reports and Annual Progress Reports must be submitted as required to FDA. Investigators will cross-reference these reports 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.

Events of Clinical Interest

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

For the time period beginning when the consent form is signed until treatment, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

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

Events of clinical interest for this trial include:
1. An overdose of Merck product, as defined in Section 5.1.11 Pembrolizumab 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.

Pregnancy and Lactation
See above in this section for additional information. Such events must be reported within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

Protocol-Specific Exceptions to Serious Adverse Event Reporting
Efficacy endpoints as outlined in this section will not be reported to Merck unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor within 24 hours and to Merck Global Safety within 2 working days either by electronic or paper media.

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

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Merck Global Safety as a SAE within 2 working days of determination that the event is not progression of the cancer under study

Hospitalization related to convenience (e.g.transportation issues etc.) will not be considered a SAE.

7.4 Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of patient safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC).

Meetings/teleconferences will be held at a frequency dependent on study accrual, and in consultation with the study Biostatistician. These meetings will include the investigators as well as protocol nurses, clinical research associates, regulatory associates, data managers, biostatisticians, and any other relevant personnel the principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, data collection, etc.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight (Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

The UNC LCCC Data and Safety Monitoring Committee (DSMC) will review the study on a regular (quarterly to annually) basis, with the frequency of review based on risk and complexity as determined by the UNC Protocol Review Committee. The UNC PI will be responsible for submitting the following information for review: 1) safety and accrual data including the number of patients treated; 2) significant developments reported in the literature that may affect the safety of participants or the ethics of the study; 3) preliminary response data; and 4) summaries of team meetings that have occurred since the last report. Findings of the DSMC review will be disseminated by memo to the UNC PI, PRC, and the UNC IRB and DSMB.

8.0 STATISTICAL CONSIDERATIONS

8.1 Study Design

This one arm, open label, phase II trial will enroll 29 patients in order to evaluate the efficacy of pembrolizumab, concomitant with and following standard of care definitive radiation, for locally advanced SCCHN patients who are not good candidates for cisplatin. Objectives include estimating PFS and OS, response rates, safety & toxicity, and quality of life in these patients. Correlative studies, based on serial blood collections and tumor samples, may be done under a separate protocol based on availability of archival diagnostic tissue (see section 1.9).

8.2 Sample Size and Accrual

In the Bonner study, median PFS (mPFS) was improved from 12.4 months to 17.1 months with the addition of cetuximab to radiotherapy. Consistent with modern practice and inclusion criteria requiring cisplatin ineligibility, we expect to accrue a somewhat sicker and more advanced population than Bonner and therefore have decreased our null hypothesis from Bonner's 12.4 months to 10 months. However, we hope to provide a larger gain in PFS as we hope that pembrolizumab will be more active than cetuximab; in particular, where cetuximab had no impact on distant control, we believe that the existing data on pembrolizumab in the metastatic setting gives reason to believe that pembrolizumab should improve distant control. We therefore hypothesize that the addition of pembrolizumab to radiotherapy will improve mPFS from 10 months to 16 months. Assuming uniform accrual, no loss to follow-up, exponentially distributed times, and a one-side alpha of 0.1, 29 patients are needed to provide 80% power to detect this level of improvement. We anticipate accrual to take 24 months, with follow-up time of at least 12 months. This calculation was made using the SWOG Statistical Center online tool for one arm survival (https://stattools.crab.org/#).

8.3 Data Analysis Plans

The primary endpoint is the estimation of PFS following standard head and neck cancer radiation concurrent with and following pembrolizumab and will be done using the Kaplan-Meier (KM) method. The KM method will also be used to estimate all other "time to event" outcomes (ex. OS, time to locoregional recurrence, time to distant metastases); median times along with rates at 20 weeks, 1 and 2 years will be reported, along with 95% confidence intervals. All patients who receive at least one dose of pembrolizumab will be included in these estimates, with censoring used as needed (ex. if a patient drops out of the study, or analysis is done before all patients have had the event of interest). The KM method, along with Log-rank tests, will be used for exploratory objectives which include comparisons between groups (ex. HPV status, biological markers).

Descriptive statistics (percentages and means/standard deviations) will be used to summarize the overall response rate (ORR), complete response rate (CRR) and quality of life scores. Depending on the availability of data, longitudinal models may be used to describe changes in quality of life scores over time. Fisher's exact tests and Wilcoxon rank sum tests will be used to explore the association of exploratory endpoints (ex. HPV status and tumor biomarkers) with response as appropriate.

Safety will be evaluated by estimating the proportion of patients who receive <95% of the intended dose of radiation (i.e., <67 Gy) and by reporting any clinically relevant toxicity (both patient and physician reported). Additionally, continuous monitoring for toxicity will be employed. Sequential boundaries will be used to monitor for unacceptable toxicity. For this study this will be defined as failing to receive at least 95% of the intended dose of XRT.

The accrual will be halted if excessive numbers of patients fail to receive at least 95% of the intended dose of XRT --that is, if the number of patients is equal to or exceeds b_n out of n patients (see table below). This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most 0.05 when the rate of failing to receive at least 95% of the intended dose of XRT is equal to the acceptable rate of 10%.
[http://cancer.unc.edu/biostatistics/program/ivanova/ContinuosMonitoringForToxicity.aspx]

Number of Patients, *n*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	-	2	3	3	3	3	4	4	4	4	5	5	5	5	5	6	6	6	6	6
Number of Patients, *n*	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35					
Boundary, b_n	6	7	7	7	7	7	7	8	8	8	8	8	8	9	9					

9.0 STUDY MANAGEMENT

9.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

9.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (NOTE: this is required if UNC holds the IND. Otherwise, the Investigator's signature documenting understanding of the protocol and providing commitment that this trial will be conducted according to all stipulations of the protocol is sufficient to ensure compliance)
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

9.3 Registration Procedures

All patients must be registered with the LCCC CPO UNCCN at the University of North Carolina before enrollment to study. To register a patient call the UNCCN at 919-966-7359 M-F 8:30am- 5pm EST. Fax (919-966-4300) or email (address to be provided at SIM) registration form, signed informed consents and all source documents to confirm eligibility.

9.4 Data Management and Monitoring/Auditing

The CPO UNCCN of the UNC LCCC will serve as the coordinating center for this trial. Data will be collected through a web based clinical research platform, OnCore®. Other study institutions will be given a password to directly enter their own data onto the web site via electronic case report forms (eCRFs). UNCCN

personnel will coordinate and manage data for quality control assurance and integrity.

All data will be collected and entered into OnCore® by Clinical Research Associates (CRAs) from UNC LCCC and participating institutions. The investigators at each site will allow monitors to review all source documents supporting data entered into OnCore®. The UNCCN Data Coordinator can be reached at 919-843-2742 or 1-877-668-0683.

As an investigator initiated study, this trial will also be audited by the Lineberger Cancer Center audit committee every six or twelve months, depending on the participation of affiliate sites.

9.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

9.5.1 Emergency Modifications

UNC and Affiliate investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC or their respective institution's IRB/IEC approval/favorable opinion.

For Institutions Relying on UNC's IRB:
For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

For Institutions Relying on Their Own IRB:
For Affiliate investigators relying on their own institution's IRB, as soon as possible after the modification has been made, the implemented deviation or change and the reasons for it should be submitted to:

- To UNC Principal Investigator for agreement
- The Affiliate institution's IRB for review and approval. (Once IRB's response is received, this should be forwarded to the UNCCN Regulatory Associate).

9.5.2 Single Patient/Subject Exceptions

For Institutions Relying on UNC's IRB:
Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the UNC Principal Investigator and the UNC IRB.

For Institutions Relying on Their Own IRB:

Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the UNC Principal Investigator and the participating institution's IRB, per its policy. Please forward the IRB response to the UNCCN Regulatory Associate by facsimile or via email within 10 business days after the original submission.

9.5.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

For Institutions Relying on UNC's IRB:
Protocol Deviations: UNC or Affiliate personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

For Institutions Relying on Their Own IRB:
In addition to adhering to the policies regarding protocol compliance set forth by your institution's IRB, the following is also required:

Protocol Deviations: In the event a deviation from protocol procedures is identified, record the deviation in OnCore®.

Protocol Violations: Any protocol violation that occurs must be reported to your IRB per institutional policies and reported to the UNCCN Project Manager within 5 days. UNC-CH will determine if the violation affects the safety of the patient and integrity of the data. Once your institution's IRB response is received, please forward to the UNCCN Regulatory Associate.

Unanticipated Problems:

Affiliate Sites:

Any events that meet the criteria for "Unanticipated Problems (UPs)" as defined by UNC's IRB must also be reported to the UNCCN Project Manager. The UNCCN Project Manager will report the event to the UNC IRB using the IRB's web-based reporting system. Examples of such UPs include a lost or stolen laptop computer that contains sensitive study information.

UNC

Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the Study Coordinator using the IRB's web-based reporting system.

9.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

For Institutions Relying on UNC's IRB:

The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

For Institutions Relying on Their Own IRB:

Investigators must submit the UNC IRB approved amendment to their institution's IRB for approval. For multi-center studies, any affiliate site must submit their informed consent revisions to the UNCCN Regulatory Associate prior to submission to their IRB.

9.7 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

9.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

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11.0 APPENDICES

11.1 Appendix A Cockcroft-Gault Formula

Estimated creatinine clearance (mL/min) = $\frac{(140\text{-age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine in mg/dL})}$

For females, use 85% of calculated creatinine clearance value.

11.2 Appendix B FACT-Head and Neck Version 4

Below is a list of statements that other people with your illness have said are important**.**
Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**

GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	<u>EMOTIONAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4

GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get	0	1	2	3	4

FUNCTIONAL WELL-BEING

		Not at all	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4

GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	<u>ADDITIONAL CONCERNS</u>	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
H&N1	I am able to eat the foods that I like	0	1	2	3	4
H&N2	My mouth is dry	0	1	2	3	4
H&N3	I have trouble breathing	0	1	2	3	4
H&N4	My voice has its usual quality and strength	0	1	2	3	4
H&N5	I am able to eat as much food as I want	0	1	2	3	4
H&N6	I am unhappy with how my face and neck look	0	1	2	3	4
H&N7	I can swallow naturally and easily	0	1	2	3	4
H&N8	I smoke cigarettes or other tobacco products	0	1	2	3	4

H&N9	I drink alcohol (e.g. beer, wine, etc.)	0	1	2	3	4
H&N 10	I am able to communicate with others	0	1	2	3	4
H&N 11	I can eat solid foods	0	1	2	3	4
H&N 12	I have pain in my mouth, throat or neck	0	1	2	3	4

11.3 Appendix C Charlson Comorbidity Index Scoring System

Table 1. Charlson Comorbidity Index Scoring System

Score	Condition
1	Myocardial infarction (history, not ECG changes only)
	Congestive heart failure
	Peripheral vascular disease (includes aortic aneurysm ≥6 cm)
	Cerebrovascular disease: CVA with mild or no residua or TIA
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease (without portal hypertension, includes chronic hepatitis)
	Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)
	Tumor without metastases (exclude if >5 y from diagnosis)
	Leukemia (acute or chronic)
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS (not just HIV positive)

NOTE. For each decade > 40 years of age, a score of 1 is added to the above score.
Abbreviations: ECG, electrocardiogram; CVA, cerebrovascular accident; TIA, transient ischemic attack; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.