SPONSOR: Sanford Research

PROTOCOL: SH MISP203

TITLE: Phase IB study of Pembrolizumab in combination with chemo radiotherapy (CRT) for locally-advanced squamous cell carcinoma of the head and neck (SCCHN)

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1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab in combination with CRT for LA-SCCHN
Trial Phase	Phase IB
Clinical Indication	Stage III-IVB Head and Neck Squamous cell carcinoma
Trial Type	Interventional
Type of control	Historical
Route of administration	Intravenous
Trial Blinding	Unblinded, open-label
Treatment Groups	(1) Pembrolizumab 200 mg days -7 (load), 15, 36, 57, 78, 99, 120, 141, cisplatin 40 mg/m2 on days 1, 8, 15, 22, 29, 36, and radiation 70 Gy fractionated over 35 days starting on day 1
Number of trial subjects	57 subjects will be enrolled (34 HPV+ subjects and 23 HPV- subjects)
Estimated enrollment period	30 months
Estimated duration of trial	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact. After a screening phase of 28 days, eligible subjects will receive treatment on Day -7 with a loading dose of the study drug. This will continue during concurrent therapy with cisplatin and radiation, which will begin on day 1. Treatment will continue until completion of therapy, documented confirmed disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the patient, noncompliance with trial treatment or procedure requirements; or administrative reasons. After the end of treatment, each patient will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the patient initiates new anticancer therapy, whichever is earlier). Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status until end of study, disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone for overall survival until death, withdrawal of consent, or the Investigator is notified by Sanford Research to discontinue follow-up.
Duration of Participation	60 months

2.0 TRIAL DESIGN

2.1 Trial Design

This is a single-arm, multi-site, open-label trial of pembrolizumab (MK-3475) used in combination with standard, cisplatin-based, definitive chemoradiotherapy (CRT) in patients with stage III-IVB squamous cell carcinoma of the head and neck (SCCHN). Approximately 57 patients with Stage III-IVB SCCHN will be enrolled to evaluate both the safety and efficacy of this novel combination. Of those 57 subjects 34 will be HPV+ and 23 will be HPV-. Subjects will not be randomized and will all receive the study treatment.

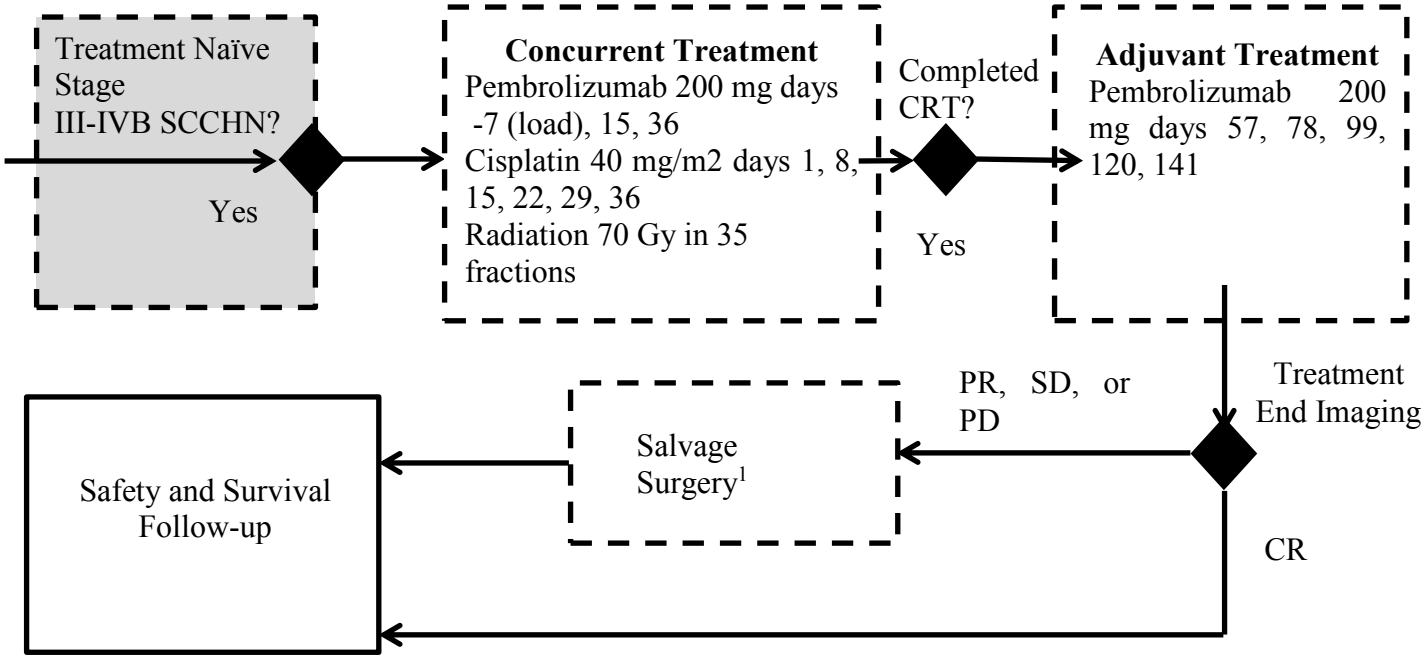
Treatment will consist of a loading dose of pembrolizumab 200 mg IV given 7 days prior to initiation of CRT (day-7). CRT with cisplatin 40 mg/m2 IV weekly and head and neck radiation at 70 Gy fractionated at 2 Gy once daily over 35 days, will begin on day 1. CRT will end on approximately day 46-50. Pembrolizumab 200 mg IV will continue following CRT in an adjuvant fashion starting on day 57 for an additional 5 doses, as tolerated, through day 141. Subjects will be evaluated for response on day 150-157 with a CT of the neck.

To support the exploratory nature of this study, correlative objectives will be explored to generate hypotheses for future research. These objectives will largely involve evaluation of the immune response during CRT, the effect of PD-1 inhibition on this response, and potential biomarkers for response to this combination. Section 6 outlines specific trial procedures.

This trial will utilize a Data and Safety Monitoring Board to monitor safety and efficacy of this novel combination. There will be an interim efficacy analysis. More details are given in section 8.7.

Efficacy, as defined primarily by complete response (CR) at treatment end and secondarily by 1- and 2-year progression-free survival (PFS), overall survival (OS), locoregional control (LRC), and cumulative incidence of distant metastases (DM) will be evaluated. These outcomes will be correlated with exploratory objectives.

2.2 Trial Diagram



[1]Salvage surgery is considered standard of care, see protocol section 7.1.2.6.3.4.

3.0 OBJECTIVE(S) & HYPOTHESIS (ES)

3.1 Primary Objective(s) & Hypothesis(es)

1. **Objective:** To determine the safety and tolerability of pembrolizumab given in combination with cisplatin-based chemoradiotherapy (CRT) in subjects with treatment naive Stage III-IVB squamous cell carcinoma of the head and neck (SCCHN).

Hypothesis: Pembrolizumab can be safely added to cisplatin-based CRT and will be well tolerated in patients with Stage III-IVB SCCHN.

2. **Objective:** To evaluate the efficacy of pembrolizumab given in combination with definitive CRT by complete response rate at treatment end in patients with HPV+ SCCHN and HPV- SCCHN.

Hypothesis: The addition of pembrolizumab to standard CRT will provide a 75% or greater CR rate in patients with Stage III-IVB HPV- SCCHN and a 90% or greater CR rate in patients with Stage III-IVB HPV+ SCCHN.

3.2 Secondary Objective(s) & Hypothesis (es)

1. **Objective:** To estimate progression-free survival (PFS), overall survival (OS), the locoregional control rate (LRC), and distant metastases (DM) rate at 1- and 2-years in subjects treated with pembrolizumab given in combination with CRT.

Hypothesis: The addition of pembrolizumab to standard CRT will show increased efficacy in terms of key survival endpoints utilized in head and neck cancer.

2. **Objective:** To determine the best overall response rate (ORR) as defined by RECIST 1.1 at treatment end imaging in subjects with Stage III-IVB SCCHN treated with pembrolizumab given in combination with CRT.

Hypothesis: The addition of pembrolizumab to standard CRT will show superior ORR compared to historical controls.

4. **Objective:** To estimate the quality of life (QOL) of subjects with Stage III-IVB SCCHN treated with pembrolizumab in combination with CRT during therapy, treatment end, and 1- and 2-years following treatment.

Hypothesis: Acute and long-term QOL of participants treated with the combination of pembrolizumab and low dose weekly cisplatin and radiation will be superior to historical controls.

5. **Objective:** To correlate ORR, PFS, OS, LRC, and DM with tumor PD-L1 expression in subjects with Stage III-IVB SCCHN treated with pembrolizumab in combination with CRT.

Hypothesis: High PD-L1 expression has correlated with responses in the metastatic setting and will correlate with key disease response and survival outcomes in the curative intent setting.

3.3 Exploratory Objectives

To determine the genomic, transcriptomic, and proteomic profile of subjects' tumors to identify gene mutations, gene amplifications, RNA-expression levels, and protein-expression levels. Additional analysis will evaluate peripheral blood immune response utilizing similar techniques. Correlations between genomic, transcriptomic, and proteomic profiles and efficacy outcomes will be assessed.

4.0 BACKGROUND & RATIONALE

4.1 Background

Merck Sharp & Dohme Corp. holds the IND 122325 for MK-3475 (pembrolizumab). Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

4.1.1 Pharmaceutical and Therapeutic Background

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar

to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

4.1.2 **Preclinical and Clinical Trial Data**

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

4.2 **Rationale**

4.2.1 **Rationale for the Trial and Selected Subject Population**

Squamous cell carcinomas of the head and neck (SCCHN) are the 6th most common malignancy diagnosed world-wide with approximately 650,000 diagnoses per year [1]. For patients with locally advanced disease, multimodality therapy with concurrent chemoradiotherapy (CRT) remains a mainstay for treatment. Despite this aggressive treatment, 5-year survival still remains less than 50% [2]. Additionally, this treatment has significant acute and late toxicities that leave survivors with permanent deficits impacting their quality of life [3]. Recent understanding of the immune clearance of head and neck cancer may provide insight into therapeutic approaches to improve survival and reduce toxicity.

Clearance of SCCHN during treatment with CRT is not only related to direct cytotoxicity, but is also dependent on the immune clearance. In a preclinical study performed by our group this was demonstrated in an HPV+ SCCHN mouse model [4]. This response is strongly dependent

on an intact CD4+ and CD8+ cellular response. Furthermore, it is apparent that radiation and cisplatin actually induces an immune response to therapy. One potential mechanism of this is by overcoming immune resistance by decreased expression of CD47 after treatment with CRT [5]. Additional recent data suggests that the PD-1:PD-L1 pathway may also play an important role in immune resistance in head and neck cancer [6].

The PD-1:PD-L1 pathway is an emerging target for immunotherapy in a number of diseases. Several monoclonal antibodies targeting this pathway are becoming clinically available. At the ASCO 2014 annual meeting, data from the KEYNOTE 012 trial utilizing pembrolizumab (MK-3475) was reported [7]. In this phase Ib study, a 60 patient cohort of recurrent and/or metastatic SCCHN patients who had progressed on prior therapy experienced a 19.6% overall response rate. Additionally, 28.6% of patients had stable disease. Many of these patients had durable (>6 month) responses or stability of disease and remain on therapy. Furthermore, the drug was well tolerated, with few single-agent dose limiting toxicities.

Based on the signal seen with single-agent pembrolizumab in this population and the understanding of immune clearance of SCCHN with CRT, the next step is evaluating this combination in primary therapy. Our lab is evaluating this combination in our immune competent HPV+ SCCHN mouse model. Using the mouse analog to pembrolizumab, we have determined that while the agent does not have significant single-agent activity, it strongly synergizes with CRT. Preliminary data from our lab displays day 100 overall survival of 58% in mice treated with PD-1 in combination with CRT versus 8% in mice treated with isotype control (IgG1) in combination with CRT ($p = 0.006$). (Data unpublished, data included in Appendix 11.6).

This preclinical finding is supported by recent clinical literature that suggests there may be synergy by adding PD-1 inhibition during primary chemoradiotherapy. Recent biomarker data suggest PD-L1 upregulation in the setting of both radiation [8,9] and cisplatin [10] alone. Additionally, a recent translational study in HPV+ SCCHN suggests that cisplatin based CRT suppresses circulating immune response by upregulating PD-1 expression on circulating CD4+ T-cells [11]. This further supports PD-1 blockade during CRT to enhance immune response during treatment in this population.

4.2.2 **Rationale for Dose Selection/Regimen/Modification**

Rationale for pembrolizumab (MK-3475) dosing:

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the MK-3475

program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

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

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

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

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

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

<u>Rationale for weekly cisplatin based chemoradiotherapy:</u>

Cisplatin based chemoradiotherapy (CRT) remains the mainstay for definitive treatment for LA-SCCHN. Various dosing regimens exist; however high-dose bolus cisplatin given at a dose of 100 mg/m2 on days 1, 22, and 43 of radiation remains the standard of care based on phase III data [12, 13]. Other dosing regimens include weekly cisplatin, daily cisplatin, and various combination regimens [14]. NCCN guidelines outline several options using cisplatin including high-dose bolus cisplatin, cisplatin in combination with 5-fluorouracil, cisplatin in combination with paclitaxel, and weekly cisplatin given at a dose of 40 mg/m2 [15]. While high-dose bolus cisplatin is the preferred choice due to randomized clinical trial data, weekly cisplatin is increasingly becoming a popular choice in clinical practice [16].

Several reasons for weekly cisplatin gaining favor exist. First of all, toxicity with high-dose bolus cisplatin is very high. Nephrotoxicity, neurotoxicity, ototoxicity, and the high emetic risk with this regimen have led to investigations into other regimens. Furthermore, many patients are unable to tolerate all three bolus doses, leading to potentially decreased efficacy [17].

While high-dose bolus cisplatin has never formally been compared head to head with weekly cisplatin in a phase III randomized trial, there have been smaller, single-institution comparisons both retrospectively and prospectively [16, 18, 19, 20]. In these studies, weekly cisplatin has been clearly better tolerated and efficacy does not seem to be impaired. Therefore, current NCCN guidelines indicate that weekly cisplatin given at a dose of 40 mg/m2 during radiation is an option, albeit with a category 2B recommendation (Category 2B: Based on a lower level of evidence, there is an NCCN consensus that intervention is appropriate).

There are several reasons while this chemotherapy backbone is appealing for combination chemoimmunotherapy. First of all, this combination is associated with a generally lower toxicity profile than bolus cisplatin. The high AE rate with high dose bolus cisplatin limits its use to only very fit patients. This lower dose, weekly preparation opens up the opportunity to treat a larger population of patients, who may be excluded from trials utilizing bolus cisplatin chemotherapy backbones.

Second, weekly cisplatin is more amenable to combination therapy. A number of cisplatin combination studies have been performed. With the evolution of targeted therapies and monoclonal antibodies, the toxicity of combination therapy with weekly cisplatin has generally been felt to be lower. Despite this, many trials using high dose bolus cisplatin in combination with these agents have been associated with very high toxicity rates. This has led many to use weekly cisplatin in novel combinations. Some studies that have been performed include the combination of weekly cisplatin with: bevacizumab[21], vandetanib[22], everolimus[23], bortezimib [24], nimotuzumab [25], among others. In general, these combinations have been well tolerated.

Based on this data, it suggests that combining weekly cisplatin with pembrolizumab will be safe and well tolerated. Furthermore, this cisplatin backbone is more amenable to steroid sparing antiemetic regimens. It is clear that corticosteroids, including dexamethasone, are immunosuppressive and may negate the effect of PD-1 inhibitors [26]. High dose bolus cisplatin carries one of the highest emetic risks [27]. Standard antiemetic guidelines from both

the NCCN and ASCO recommend the use of high dose corticosteroids on day 1 through 4 when treating with high emetic risk chemotherapy [27, 28]. Current combination chemoimmunotherapy studies using PD-1 inhibitors often limit dexamethasone dose to no more than 4 mg at a time. This is far below what is recommended for standard high emetic risk prophylaxis. While low-dose weekly cisplatin still may pose a significant emetic risk, our institutional standard is to treat the regimen as moderate emetic risk. This affords the option to eliminate corticosteroids from the antiemetic management. Use of steroids sparing antiemetics may be effective enough to control nausea with this regimen.

Rationale for combination regimen

As outlined in the study schema, treatment is outlined as two separate periods: Concurrent treatment and adjuvant treatment. Pembrolizumab will be administered initially as a loading dose, similar to what is done with cetuximab-based CRT [29]. There are several reasons for this loading dose. First, this loading dose will allow for an initial evaluation for potential infusion reactions and acute immune related adverse events prior to initiation of standard CRT. This will support the safety component of this study, in that patients with severe immune adverse events at the start of therapy will not have their standard treatment impacted, as further doses of pembrolizumab would be held and/or appropriate supportive medications could be initiated.

Secondly, the rationale behind the loading dose is to allow the drug time before the initiation of chemoradiation to invoke an immune response. While "flare responses" are fairly uncommon in head and neck cancer, these can be seen. A loading dose of this drug will allow some time for recovery until standard CRT is started. Logistically, this loading dose should not be an issue for routine clinical care, due to the time needed to begin radiation planning and initiation. This allows for a window of time to utilize the loading dose. Furthermore, it mirrors standard clinical practice when using cetuximab-based CRT.

The rationale for doses given during concurrent treatment is based on preclinical and clinical literature. High PD-L1 expression has strongly correlated with a response to pembrolizumab [30]. While patients with low or no PD-L1 expression can still respond to the drug, response rates are much higher in those with high expression. Recent literature suggests that both cisplatin and radiation independently cause upregulation of PD-L1 [9, 10]. In the absence of PD-1 inhibition, this could lead to decreased immune clearance and may be a biomarker of chemoradioresistance. Based on the predictive nature of PD-L1 expression on response to pembrolizumab, treatment during a period of high PD-L1 expression makes perfect sense. Further supporting this is a recent clinical study demonstrated that cisplatin-based CRT suppresses circulating immune response by upregulating PD-1 expression nearly 2.5-fold on circulating CD4+ T-cells [11]. Overall circulating T-cells were suppressed by the end of CRT and there was an increase in myeloid derived suppressor cells (MDSCs), thus creating an immunosuppressed phenotype by the end of therapy. Adding PD-1 inhibition following standard CRT may be efficacious, however it may be equally or more efficacious to add treatment at the beginning and during concurrent therapy before the circulating T-cell pools have been depleted and prior to the emergency of the immunosuppressive environment.

This regimen also consists of an adjuvant treatment period with pembrolizumab that will continue every 3 weeks until day 100 post-treatment imaging. A great deal of inflammation will be occurring in the tumor microenvironment during this time and optimization of immune clearance with pembrolizumab will be important. It is possible that the greatest amount of tumor clearance will occur during this time; therefore, it is vital to include this adjuvant period.

The ultimate rationale behind this combination is to determine if this combination is as safe and efficacious as the gold standard of high-dose bolus cisplatin. This current standard of care has significant toxicity and carries substantial acute and late morbidity for patients. If the combination of pembrolizumab with weekly cisplatin and radiation is well tolerated and equally or more efficacious than the current standard of care, this could replace high-dose bolus cisplatin as the preferred treatment for LA-SCCHN. Depending on the efficacy and analysis of biomarkers, the potential for "de-escalation" therapy using this chemoimmunotherapy backbone may be presented.

4.2.3 **Rationale for Endpoints**

4.2.3.1 **Safety and Efficacy Endpoints**

Safety and efficacy are the primary endpoints for this study. Safety is an important endpoint for a study like this for a number of factors. First of all, the inflammatory events surrounding chemoradiation, while potentially allowing for improved immune clearance with pembrolizumab, may end up causing more toxicity. The PD-1: PD-L1 pathway is important in normal, healthy individuals in protecting from autoimmunity during inflammatory events. As CRT will induce an inflammatory event in the head and neck region, one can surmise that PD-L1 and PD-1 upregulation may be a normal response meant to protect from autoimmune events. Evaluation of safety during and following this period is paramount to understanding the role of PD-1 inhibitors combined with CRT. While a certain level of toxicity is expected with this combination, special attention will be paid to immune-related toxicities and exacerbation of known CRT related toxicities. If this combination is not felt to be safe, it would not be recommended to move forth with further evaluation.

Efficacy is the co-primary endpoint for the study. This endpoint is important to estimate the clinical benefit of this combination. If there is little to no added benefit with this combination, it would not be recommended to move forth with additional studies utilizing this combination. If the treatment is efficacious, it would be reasonable to consider phase III testing of this combination, comparing it to high-dose bolus cisplatin.

Complete response rate was chosen as the primary efficacy measure. While progression-free survival may be a reasonable alternative to this efficacy measure, complete response rate was chosen based on several factors. First, this was the efficacy measure in preclinical studies that suggested this combination was efficacious. Second, this outcome can be compared to the Intergroup Trial [13], which evaluated high-dose bolus cisplatin in a phase III setting. In this study, imaging and clinical response were used to determine response rate. The complete response rate in those treated with high-dose bolus cisplatin was 40.2% among 87 analyzable patients. While the imaging and response criteria from that study does not directly match what

is proposed in this study, we feel the response criteria documented is stricter and mirrors what is done in standard clinical practice today, to follow response in patients treated with CRT. This endpoint is supported by the fact that patients without a CR will have salvage surgery. This will give a true pathologic response. A second analysis looking at pathologic and radiographic response will be performed. This will give a second assessment of efficacy of this combination. The main purpose for using response as an assessment is for rapid analysis of the efficacy of this regimen. Due to the nature of head and neck cancer treatment and the interest in improving therapy, it is important to rapidly estimate efficacy and move forward with phase III testing if signals are present.

Although they are not primary endpoints, important survival and response endpoints will be followed as secondary endpoints during this study. These will include progression-free survival, overall survival, locoregional control (LRC) rate, distant metastasis (DM) rate, and overall response rate (ORR). While the study is not powered for these endpoints, they will be compared to historical data from similar head and neck studies. If these are found to be superior to historical data and the analysis is statistically sound, these endpoints may be considered when deciding whether to move forward with further evaluation of this combination. As these data points take longer to mature, we have opted to have them serve as secondary endpoints and keep CR rate as the primary measure of efficacy.

4.2.3.2 **Pharmacokinetic, Biomarker, and Patient Report Outcomes Research**

There are ongoing clinical trials evaluating pembrolizumab in combination with platinum-doublet therapy in non-small cell lung cancer and in other chemotherapy combination studies [31]. This will be the first study looking at pembrolizumab in combination with weekly cisplatin chemotherapy. Despite this, based on data from other combination studies, the risk for a drug-drug interaction is extremely low. Furthermore, pembrolizumab has been utilized with cisplatin at varying doses in a number of studies with accompanying pharmacokinetic data. As a result, pharmacokinetic data will not be obtained during this study. Additionally, as it is felt there is reasonable data available to understand the risk of anti-drug antibodies with this combination. Therefore, this will also be excluded from this protocol.

PD-L1 expression may be an important factor in efficacy. Current data supports high PD-L1 expression as a correlate of response to therapy. While patients with no or low expression may still respond to pembrolizumab, the response rates are significantly higher for those with high expression. As we venture into multimodality therapy with chemotherapy and radiation, it will be important to see if baseline expression of PD-L1 correlates with a response. As previously mentioned, data is emerging that suggests altered PD-L1 expression during both chemotherapy and radiation. While we will not be performing biopsies during therapy, the baseline PD-L1 expression may be important to see if this biomarker maintains its predictive nature in the setting of chemoradiation. There is the potential that the biomarker will not continue to predict response, as even non-expressers or low expressers at baseline, may develop enhanced responses during CRT. It will be important to evaluate PD-L1 expression to generate hypotheses for future biomarker research.

A final supportive outcome of importance is patient-related outcomes (PRO). High-dose bolus cisplatin is highly toxic and leads to severe acute and late effects for patients. Survivors of head and neck cancer experience some of the most severe late effects from therapy [32]. During treatment, the majority of patients will require feeding tubes as they will develop severe mucositis, dysphagia/odynophagia, nausea/vomiting, loss of appetite, xerostomia/sialorrhea, and malnutrition [12]. Fatigue, difficulties with speech, and inability to eat can affect mood. It may take anywhere from 12-36 months for most patients to return back to an acceptable baseline quality of life (QOL) [33]. Some patients will never return to a self-rated acceptable QOL. The factors degrading QOL are complex, but include psychosocial symptoms and chronic somatic changes related to the disease and associated treatment [34]. Many feel that low-dose weekly cisplatin may be better tolerated and have improved QOL indices [17]. We feel that QOL is an extremely important endpoint to evaluate when developing a novel combination as proposed. This is important, as even if efficacy is improved, if QOL is significantly degraded, it may not be worthwhile to move forward with further testing. Fortunately, we have QOL data, using the Functional Assessment of Cancer Therapy Head and Neck (FACT H&N) survey, from approximately 50 patients treated with standard of care, high-dose bolus cisplatin in this setting for comparison at approximate time points as outlined in this study [35]. We propose using the same QOL survey for this study. While it is not a head to head comparison in a randomized trial, it does provide insight into how this combination may be tolerated in a phase III comparison to standard therapy.

4.2.3.3 **Exploratory Research**

As previously mentioned, we have data from a randomized phase 2 trial in this setting, in this same patient population [35]. The study utilized high-dose bolus cisplatin 100 mg/m2 on days 1, 22, and 43 with or without the agent dichloroacetate (DCA). From this study, we have historically banked specimens from 40-50 patients undergoing primary CRT. These specimens include tumor RNA/DNA (freshly isolated), tumor blocks of primary and metastatic nodal specimens, peripheral immune cells isolated to remain live and functional. Quality of life analyses, response data, and survival data were also prospectively collected and can be correlated to outcomes. These data will be used as a control to ascertain changes seen with the addition of PD-1 inhibition as proposed in this study. This data, combined with the correlative studies performed during this study, can provide valuable insight into biomarkers for treatment response, targets for future therapy, and other potential factors that may impact efficacy and safety, as we enter the field of chemoimmunoradiotherapy.

While this is still developing in this field, several of the key areas of exploratory research in this setting include: circulating immune cell analysis, tumor infiltrate immune cell analysis, the HPV specific immune response [11], and tumor genomic alterations [36]. We have the capability to collect specimens and evaluate each of these factors during and following CRT. As previously mentioned, we have experience with these procedures from a prior study in a similar population. Furthermore, our cancer biology COBRE grant funding and core facilities will help fund and assist in this testing.

4.2.3.4 **Exploratory Molecular Profiling and Analysis and its Rationale**

Genomic sequencing of tumor cells from tissue relative to non-tumor cells from whole blood will be profiled to identify the genomic variances that may contribute to response or disease progression and provide an understanding of molecular abnormalities. RNA sequencing will be conducted to provide expression data and give relevance to DNA mutations; Quantitative proteomics analysis will be conducted to determine the exact amounts of specific proteins and to confirm expression of genes that are correlative of response and disease progression. Flow cytometry and T-cell gene analysis utilizing similar techniques will be utilized to evaluate peripheral blood immunocyte response during therapy. All genomic, transcriptomic, and proteomic molecular analyses will be retrospective and exploratory.

4.2.3.5 **Preliminary Results and Rationale for Expansion Cohort**

The current study has enrolled 27 patients from November 18, 2015 to August 6, 2016. The study is currently on hold for an interim safety and efficacy analysis. As of the data lock on September 14, 2016, 20 (74.1%) patients with HPV positive (p16 positive) disease and 7 (15.9%) with HPV negative (p16 negative) disease have enrolled. Early response data in imaged patients (n=9), shows a CR (CT and/or PET or pathologic CR on salvage surgery) in 8/8 (100%) of HPV positive patients and a PR in the single HPV negative patient. We anticipate easily hitting our primary endpoint of CR rate >60% in our HPV positive population based on these early results. However, based on our lack of HPV negative patients, it is unclear what responses will be seen.

Recent data analysis of an internal study (NCT01386632) using standard of care high-dose cisplatin (100 mg/m2 on days 1, 22, and 43) in a similar cohort of patients was performed. Distinct differences in response were seen in the HPV+ and HPV- groups, which mirror efficacy findings in similar studies. This analysis has revealed that 20 of 27 (74%) of evaluable patients with HPV positive disease achieved a CR (based on 3-month post-radiation CT and/or PET or subsequent salvage surgery). In the same study, the evaluable patients in the HPV negative cohort had 6 of 12 (50%) achieving the same CR endpoint.

Due to the historically good responses in HPV positive disease and the early findings in our current HPV positive cohort, we propose evaluation of efficacy separately in the HPV positive and HPV negative cohorts. As a result, we propose adding expansion cohorts after the interim analysis to explore efficacy in each of these unique populations. Addition of both HPV negative and HPV positive patients will provide further insight into efficacy of this novel combination.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male and female patients with TNM clinical stage III, IVA, or IVB squamous cell carcinoma of oral cavity (excluding lip), oropharynx, hypopharynx, and larynx eligible for curative-intent treatment. A total of 57 patients will be enrolled with 34 of those patients being HPV-positive and 23 patients being HPV-negative. Enrollment to each sub-category will end when the target is met.

5.1.2 Subject Inclusion Criteria

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

1. Have histologically or cytologically-confirmed head and neck squamous cell carcinoma of the oral cavity (excluding lip), oropharynx, hypopharynx, or larynx.

2. Have TNM clinical stage III, IVA, or IVB disease. Can have T_0 disease if evaluation of pathology indicates an origin of one of the above sites. (See criteria 1)

3. Be eligible for curative-intent concurrent chemoradiation therapy

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

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

6. Have a known p16 status by immunohistochemical stain

    a. HPV positivity is defined by p16 IHC staining of > 70% of tumor cells (strong and diffuse nuclear and cytoplasmic staining)

    b. For cases that are indeterminate or if p16 testing cannot be accurately performed, HPV positivity can be confirmed by high-risk HPV DNA Testing which covers the following HPV subtypes: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68.

7. Have measurable disease based on RECIST 1.1

8. Be willing to provide tissue from a recently obtained core or excisional biopsy of a tumor lesion. *Recently-obtained is defined as a specimen obtained up to 60 days prior to enrollment. Subjects for whom recently-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from Sanford Research.*

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

10. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 days of treatment initiation (Day -7).

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
[a]Creatinine clearance should be calculated per institutional standard.	

11. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

12. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

13. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

5.1.3 **Subject Exclusion Criteria**

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

1. Patients may not be receiving any other investigational agents, chemotherapy, immunotherapy, radiotherapy, or molecular targeted agents within 4 weeks of the start of the study treatment.

2. Prior treatment with radiation to the head and neck

3. Patients with TNM Stage IVC disease

4. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.

5. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

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

7. Hypersensitivity to pembrolizumab or any of its excipients.

8. Has had a prior anti-cancer monoclonal antibody (mAb) 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.

9. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy.

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

11. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

12. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

13. Has known history of, or any evidence of active, non-infectious pneumonitis.

14. Has an active infection requiring systemic therapy.

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

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

17. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120days after the last dose of trial treatment.

18. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

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

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

21. Has received a live vaccine within 30 days of planned start of study therapy.
Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

5.2 Trial Treatments

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

Table 2 Trial Treatments

Drug	Dose	Dose Frequency	Route	Regimen	Use
Pembrolizumab	200 mg	Days -7, 15, 36, 57, 78, 99, 120, 141	Intravenous	Every 3 weeks starting on day -7 during CRT; then every 3 weeks following CRT ending on day 141.	Experimental
Cisplatin	40 mg/m2	Days 1, 8, 15, 22, 29, 36	Intravenous	Weekly starting on day 1	Standard of care
Radiation	2 Gy	Daily (Monday-Friday) starting on day 1	3D or IMRT	Day1-50 (approximate*) for a total of 35 treatments	Standard of care

*Note: If the subject experiences radiation treatment delays the active treatment phase can extend beyond 7 weeks.

Study treatment begins on day -7 with a loading dose of pembrolizumab. Day 1 signifies the start date of CRT. Both cisplatin and radiation should begin on day 1. CRT will end on the last day of radiation, which is when the cumulative dose reaches 70 Gy.

Patients will be closely monitored for treatment-related adverse events, especially hypersensitivity reactions, during the infusion and the post-infusion per local guidelines. For the duration that patients are on study therapy, adverse event monitoring will be done and recorded. Patients will be evaluated for adverse events at each visit and are to be instructed to call their physician to report any clinically significant adverse events between visits.

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

5.2.1 **Dose Selection/Modification**

5.2.1.1 **Dose Selection**

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

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

5.2.1.2 **Dose Modification**

The investigator may attribute each toxicity event to the study drug (pembrolizumab), cisplatin, or radiation alone, if appropriate. If a dose reduction for toxicity occurs, the dose of that agent may not be re-escalated. Dose modifications for additional rounds of treatment are based on the most recent dose utilized previously. Dose modifications for pembrolizumab (section 5.2.1.2.1), cisplatin (5.2.1.2.2) and radiation (5.2.1.2.3) are outlined below.

5.2.1.2.1 Dose Modification for Pembrolizumab

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

Table 3 Dose Modification Guidelines for Pembrolizumab-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 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)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 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
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	2-4	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability 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[2]	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.

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

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

5.2.1.2.2 Dose Modification for Cisplatin

Investigators must use cisplatin for this protocol. Substitutions to carboplatin will not be permitted. If toxicities occur, dose reductions as outlined in Tables 3.1 and 3.2 should be performed.

Cisplatin will not be given until the ANC exceeds 1000/mm3 and the platelet count exceeds 75,000/mm3. Myeloid growth factors can be used per local guidelines.

Complete blood count, differential and platelets will be checked weekly during therapy. Cisplatin dose will be reduced for nadir WBC or platelet count as follows:

Table 3.1 – Cisplatin modifications based on Hematology Parameters

Nadir			% of 100%
ANC		**Platelet**	**Cisplatin Dose to Give**
≥ 1000	And	>75,000	100% (dose level 0)
500 – 999	Or	50 – 75,000	80% (dose level -1)
< 500	Or	< 50,000	60% (dose level -2)

Cisplatin will only be given if the serum creatinine is < 1.6 mg/dl.
Reduce cisplatin dose for transient rises in creatinine as follows:

Table 3.2 Cisplatin modifications based on Creatinine Peak

Creatinine Peak	**Cisplatin Dose to Give**
≤ 1.6	100% (dose level 0)
>1.6 – 4.0	80% (dose level -1)
> 4.0	60% (dose level -2)

In individuals whose creatinine does not come back down to <1.6 mg/dl, cisplatin should continue to be held.

Neurotoxicity:
Grade 3 hearing loss in the speech frequency range is an indication to discontinue cisplatin. Significant (grade 3) myopathy, weakness, or neuropathy; seizure or paralysis should prompt discontinuation of cisplatin and contact with the principal investigator.

Other adverse events:
Any other grade 4 adverse events, not previously outlined above, will result in decreasing the next weekly dose of cisplatin to 80% (dose level -1). If any grade 4 event persists beyond dose reduction to 60% (dose level -2), cisplatin will be permanently discontinued for the duration of the study.

Dose reductions for grade 3 events, not previously outlined above, will be permitted, but are at the discretion of the individual treating physician. Dose modifications should be performed as: Dose level -1 = 80% dose, Dose level -2 = 60% dose, dose level -3 = hold further cisplatin. Treatment-related grade 3 mucositis, skin toxic effects, xerostomia, dysphagia, and anorexia, are expected toxicities, and dose reduction is not recommended, but will be permitted.

Dose re-escalations are not permitted.

5.2.1.2.3 Dose Modification for Radiation

Reversible radiation mucositis is expected to develop in the majority of patients. This will commonly manifest as Grades I to III in severity. In those rare cases of Grade IV mucositis, radiation can be interrupted for up to5 consecutive radiation treatment days until the reaction subsides to Grade III. However, every effort should be made to keep this treatment break as short as possible. If Grade IV mucositis occurs, systemic chemotherapy should also be held until the reaction subsides to Grade III and then radiation and chemotherapy are resumed.

Toxicities: Common radiation toxicities include mucositis, fatigue, weight loss, regional alopecia, xerostomia, hoarseness, transient ear discomfort, hypogeusia, dysgeusia, dysphagia, and skin erythema and desquamation within the treatment fields. Less common long-term radiation toxicities include hypothyroidism, loss of hearing, chronic swallowing dysfunction requiring permanent feeding tube, and cervical fibrosis. Much less common radiation toxicities include mandibular osteoradionecrosis (<5% incidence with attention to a full dental evaluation as part of pre-treatment planning), and cervical myelopathy (<1% with restriction of spinal cord dose to < 45 Gy).

5.2.1.3 Timing of Dose Administration

Trial treatment should be administered after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 4 days after the scheduled Day -7 treatment start date due to administrative reasons. Additional treatments may be delayed as outlined in Section 6.0.

5.2.1.3.1 Pembrolizumab

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

On days in which cisplatin is to be administered the same day as pembrolizumab, pembrolizumab should be administered prior to the cisplatin. On days when pembrolizumab is to coincide only with radiation, pembrolizumab can be given prior to or after radiation.

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

5.2.1.3.2 Cisplatin

Cisplatin will be administered weekly (every 7 days) starting on day 1 of CRT. Treatment cannot begin until all study procedures and assessments are completed as outlined in the Trial Flow Chart (Section 6.0).

Cisplatin is to be given as a dose of 40 mg/m2 using an infusion duration of 60 minutes (or infusion duration according to local practice).

5.2.2 Radiation

IMRT planning will be used for this study.

5.2.2.1 IMRT

IMRT will be given as 70 Gy in 35 fractions over approximately 7 weeks. The primary tumor and involved nodes (PTV_{HD}) will receive 2 Gy per fractions and subclinical disease sites (PTV_{ID}) will receive 1.8 Gy per fraction. The total doses will thus be 70 Gy and 63 Gy, respectively. When desired, PTV_{ID} can receive 1.6 Gy per fractions to a total dose of 56 Gy (PTV_{LD}).

All plans must be normalized such that 95% of the volume of the PTV_{HD} is covered with the prescription dose of 70Gy. Additionally:

- No more than 20% of the PTV_{HD} should receive ≥ 110% of the prescribed dose;
- No more than 1% of any PTV_{HD} or PTV_{ID} should receive ≤ 93% of the prescribed dose;
- No more than 1% or 1 cc of the tissue outside the PTVs should receive ≥ 110% of the prescribed dose to the PTV_{HD}.

5.2.2.2 Technical Factors

Photon beams of ≥ 4 MV and/or electron beams from 6-25 MeV are required. Treatment distance must be ≥ 80 cm SAD for isocentric techniques.

IMRT: Megavoltage equipment capable of delivering intensity modulated beams using a step-and-shoot technique with a multileaf collimator or using dynamically moving leaves. Additionally, a binary multileaf collimator or tomotherapy can be used to modulate the beam. Other techniques, e.g. physical compensators, are acceptable as long as dose specifications and constraints are satisfied.

5.2.2.3 Immobilization, Simulation, and Localization

5.2.2.4 Immobilization

The use of a thermoplastic head and shoulder mask is mandatory for IMRT. The margins used for expansion of the CTVs to PTVs are discussed in Section 5.2.2.3.3.

5.2.2.5 Planning CT scan

A treatment planning CT scan is mandatory for defining target volumes (see Section 5.2.2.6). CT scan thickness should be at most 0.3 cm for IMRT. The treatment planning CT scan should be acquired with the patient in the same position and using the same immobilization device as for treatment. All tissues receiving irradiation should be included in the CT scan.

5.2.2.6 Treatment Planning/Target Volumes

CT based treatment planning is mandatory for every patient. For IMRT, the treatment plan used for each patient will be based on an analysis of the volumetric dose, including dose-volume histogram (DVH) analyses of the PTV (CTV with a 5 mm margin) and critical normal structures. An "inverse" planning with computerized optimization should be used.

Gross Tumor Volume (GTV) represents the region judged to contain gross primary tumor or involved node(s) based on clinical and endoscopic examinations, CT scan, and, when applicable, other imaging techniques. Grossly positive lymph nodes are defined as any lymph nodes > 1 cm or nodes with a necrotic center.

Clinical Target Volume (CTV) is defined as the GTV plus areas considered at risk for containing microscopic disease delineated by the treating physician. CTV_1 represents GTV plus a margin of generally 1 cm and CTV_2 represents GTV with a margin of about 2 cm and nodal regions to receive elective irradiation. When the tumor is infiltrative (endophytic) or when the border is ill defined, it might be desirable to deliver an intermediate dose (e.g., 59-63 Gy) to a volume (CTV_{INT}) that is slightly larger than CTV_1. The CTV margins can be narrower when GTV is in the proximity of the spinal cord or critical normal tissues.

Planning Target Volume (PTV_{HD}, PTV_{ID}, PTV_{LD}) represents an additional margin around CTV_1 and CTV_2 to compensate for the variability of treatment set up and internal organ motion. A minimum margin of 0.5 cm around the CTV is required in all directions to define each respective PTV, except for situations in which the CTV is adjacent to spinal cord or other critical normal tissues. In such situations, the margin can be reduced judiciously. A minimum margin of 3 mm can be used in all directions as long as an institution implements a study to define the appropriate magnitude of the uncertain components of the PTV.

5.2.2.7 Critical Structures

Spinal cord: A margin of 0.5-1cm around the spinal cord may be added to create a Planning Organ at Risk Volume (PRV). The dose to any point within the spinal cord should not exceed 48 Gy to any volume larger than 0.03 cc (approximately equivalent to a 3x3x3 mm cube).

Parotid glands: When using IMRT, the objective is to limit the mean dose to at least one gland to ≤ 26 Gy; alternatively at least 20 cc of the combined volume of both parotid glands to < 20 Gy or at least 50% of one gland to <30 Gy.

Glottic larynx: In patients with oropharyngeal carcinoma without extension to the larynx, placing the isocenter just above the arytenoids and irradiating the lower neck with an anterior matching field with larynx block can minimize the dose to the glottic larynx. Alternatively, the dose to the larynx should be kept <45 Gy whenever feasible.

Brachial plexus: The dose to the brachial plexus must be limited to ≤ 60 Gy in patients with level IV node(s).based on a dose distribution corrected for heterogeneities.

Unspecified tissue outside the target volumes: ≤ 100% of the dose prescribed to CTV_1. No more than 5% of the non-target tissue can receive greater than the dose to CTV_1.

5.2.2.8 **Documentation Requirements**

Portal image of each field of 3-D radiotherapy or orthogonal images that localize the isocenter placement of IMRT must be obtained on the first day of therapy.

Weekly verification or orthogonal images are required.

Isodose plans for IMRT and DVHs of GTV, CTVs, and critical normal structures for IMRT.

5.2.2.9 **Compliance Criteria**

Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Missed treatments due to holidays or logistic reasons can be compensated for by delivering additional BID treatments with a minimum interfraction interval of 6 hours or by treating on a Saturday or Sunday.

Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and ideally, should not exceed 5 treatment days at a time and 10 treatment days in total. Any treatment break*(s)* exceeding two treatment days for reasons other than toxicity/illness will be considered a protocol deviation.

Plan normalization should provide coverage of 95% of the volume of the PTV of the GTV (PTVHD) with the prescribed dose of 70 Gy. No more than 1% of the volume of the PTV_{HD} should receive less than 64 Gy. Additionally, no more than 10% of the PTV of the GTV should receive more than 76 Gy, and no more than 5% of this volume should receive more than 79 Gy. These numbers describe the DVH shown in the figure below with the diamond shaped symbols. Obviously, better DVHs (i.e., with smaller amounts of either underdose or overdose) are preferable.

A region of “minor deviation” is also defined in the figure as the DVH represented by the square symbols. Deviations of this magnitude are not desirable, but will be deemed acceptable.

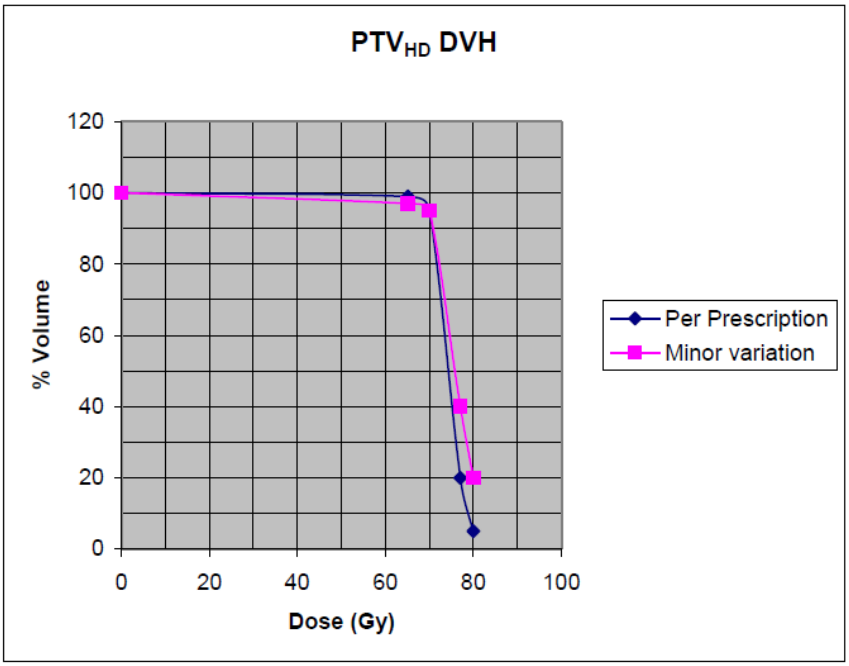
That is, a DVH with at least 97% of the volume receiving 64 Gy is acceptable as a minor deviation.

Additionally, as a minor deviation for the overdose region, as much as 40% of the PTV_{HD} volume can receive 76 Gy and up to 10% of this volume can receive 79 Gy. DVHs for the PTVHD falling outside the limits for a minor deviation (i.e., increased under or overdose) will be scored as unacceptable "major deviations."

The DVHs for the other target regions should deliver the prescribed dose, as much as possible, to at least 95% of the volume of that PTV.

Overall Evaluation	Radiotherapy Prolongation	Total Dose Variation IMRT**
Per Protocol	≤5 days	See parameters in the figure below
Minor Variation (Acceptable)	6-10 days	See parameters in the figure and table below
Major Deviation (Unacceptable)	>10 days	Deviations greater than presented in the table and figure below

**Note: For IMRT, prescription dose is the isodose surface that encompasses at least 95% of the planning target volume (PTV) with no more than 10% of any PTV_{HD} receiving ≥ 110% of the prescribed dose and no more than 1% of any PTV_{HD} and PTV_{ID} receiving ≤ 93% of the prescribed dose.



Dose (Gy)	Per Prescription	Minor variation
65	99%	97%
70	95%	95%
77	20%	40%
80	5%	20%

5.3 Trial Blinding/Masking

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

5.4 Randomization or Treatment Allocation

The study is non-randomized. There is only one treatment arm. All subjects will receive the study treatment.

5.5 Stratification

There are two separate cohorts of subjects in this clinical trial. Thirty-four of the 57 subjects will be HPV+ while the remaining 23 subjects will be HPV-.

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5.6 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 Principal Investigator. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.6.1 Acceptable Concomitant Medications

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

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

5.6.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy not specified in this protocol
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the study Principal Investigator or designee.

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

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

5.7 Rescue Medications & Supportive Care

5.7.1 Supportive Care Guidelines for Pembrolizumab

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

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 5.2.1 for dose modification.

- It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.
- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- **Diarrhea/Colitis**:
  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and

electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

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

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

- **Hypophysitis**:

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

- **Hyperthyroidism or Hypothyroidism**:
  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

  - **Grade 2** hyperthyroidism events (and **Grade 3-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid

taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

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

- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Management of Infusion Reactions: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

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

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., 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 (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
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.		

5.7.2 **Supportive Care Guidelines for Cisplatin**

Based on local standard practices the chemotherapy regimen is considered moderate emesis potential. Prevention and/or treatment of nausea and vomiting should be managed with the following regimen initially:

Prior to each cisplatin dose:

1. Fosaprepitant 150 mg IV day 1 or aprepitant 3 day pack (125 mg day 1, 80 mg days 2 and 3)
2. Palonosetron 0.25 mg IV day 1

Additional scheduled antiemetic support can include (per investigator discretion):

1. Ondansetron 8 mg two times a day starting 1 day following palonsetron
2. Prochlorperazine 10 mg IV/PO 3-4 times per day
3. Olanzapine 5-10mg PO days 1-4
4. Granisetron transdermal patch 3.1mg/day; maximum duration of patch is 7 days
5. Lorazepam 0.5-2mg PO/IV every 4-6 hours
6. H2 blocker or proton pump inhibitor

Additional as needed antiemetics can be used per local standards. However, due to the immunologic nature of this trial, corticosteroids, including dexamethasone should not be used unless Grade 4 nausea occurs. If this occurs, dexamethasone 4 mg IV/PO can be used as a premedication for cisplatin. If Grade 4 nausea still occurs, despite dexamethasone 4 mg IV/PO, additional corticosteroid can be used after discussion with the principal investigator.

Please refer to the product label or local standards of care for additional cisplatin supportive measures.

Hydration and electrolyte replacement may be utilized per the discretion of the treating physician provided adequate pre/post cisplatin hydration is achieved and renal function remains adequate.

5.7.3 **Supportive Care Guidelines for Radiation**

Please refer to local standards of care for additional supportive measures for radiation.

5.8 **Diet/Activity/Other Considerations**

5.8.1 **Diet**

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

5.8.2 **Contraception**

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.2-Reporting of Pregnancy and Lactation to Sanford Research and to Merck. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.8.3 **Use in Pregnancy**

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

been completed or terminated. The outcome of the pregnancy will be reported to Sanford Research and to Merck without delay and within 24 hours to Sanford Research and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

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

5.8.4 **Use in Nursing Women**

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

5.8.4.1 **Pembrolizumab**

It is unknown whether pembrolizumab is excreted in human milk.

5.8.4.2 **Cisplatin**

Cisplatin has been reported to be found in human milk; subjects receiving Cisplatin injection should not breast-feed.

5.9 **Subject Withdrawal/Discontinuation Criteria**

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

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment

- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

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

5.10 Subject Replacement Strategy

A subject who discontinues from the trial during the active treatment for reasons other than AE/SAE or progression will be replaced.

5.11 Clinical Criteria for Early Trial Termination

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

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

6.0 TRIAL FLOW CHART

6.1 Screening and Concurrent Treatment Phase

	Screening Visit	Treatment Days[1]								
Treatment Day	**-36 to -8**	**-7**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**
Scheduling Window[2] (days)		**+4**	**+/-2**	**+/-2**	**+/-2**	**+/-2**	**+/-2**	**+/-2**	**+/-2**	**+/-2**
Administrative Procedures										
Informed consent	**x**									
Informed consent correlative research	**x**									
Inclusion/exclusion criteria	**x**									
Demographics and medical history	**x**									
Prior and concomitant medications	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Disease specific details	**x**									
Clinical Procedures and Assessments										
Adverse Events		**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Full Physical Exam	**x**									
Directed Physical Exam		**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	

	Screening Visit	Treatment Days[1]								
Treatment Day	**-36 to -8**	**-7**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**
Scheduling Window[2] (days)		**+4**	**+/-2**	**+/-2**	**+/-2**	**+/-2**	**+/-2**	**+/-2**	**+/-2**	**+/-2**
Vitals and Weight[19]	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	
ECOG PS	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	
Study Treatments										
Pembrolizumab		**x**			**x**			**x**		
Cisplatin			**x**	**x**	**x**	**x**	**x**	**x**		
Radiation[3]			**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Laboratory Procedures/Assessments (local laboratory testing):										
Pregnancy Test[4]	**x**									
CBC with differential	**x**	**x[15]**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Serum Chemistry Panel[5]	**x**	**x[15]**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Uric Acid	**x**	**x[15]**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Magnesium, Phosphorus, LDH	**x**	**x[15]**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
T3, FT4, TSH	**x**				**x**			**x**		

	Screening Visit	Treatment Days[1]								
Treatment Day	**-36 to -8**	**-7**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**
Scheduling Window[2] (days)		**+4**	**+/-2**	**+/-2**	**+/-2**	**+/-2**	**+/-2**	**+/-2**	**+/-2**	**+/-2**
Urinalysis	**x**				**x**			**x**		
P16 testing[6]	**x**									
Imaging										
Tumor Imaging (CT neck[12], PET[14])	**x**									
Correlative Study Procedures										
Tumor tissue collection[7]	**x**									
Blood for correlative studies[10]		**x**			**x**			**x**		
Patient Reported Outcomes (PRO)										
FACT H&N[11]		**x**						**x**		

6.2 Adjuvant Treatment Phase

	Treatment Days[1]					Treatment End
Treatment Day	**57**	**78**	**99**	**120**	**141**	**150**
Scheduling Window (days)[2]	**-3/+7**	**-3/+7**	**-3/+7**	**-3/+7**	**-3/+7**	**-7/+14**
Administrative Procedures						
Prior and concomitant medications	**x**	**x**	**x**	**x**	**x**	**x**
Clinical Procedures and Assessments						
Adverse Events	**x**	**x**	**x**	**x**	**x**	**x**
Directed Physical Exam	**x**	**x**	**x**	**x**	**x**	**x**
Vitals and Weight	**x**	**x**	**x**	**x**	**x**	**x**
ECOG PS	**x**	**x**	**x**	**x**	**x**	**x**
Study Treatments						
Pembrolizumab[17,18]	**x**	**x**	**x**	**x**	**x**	

	Treatment Days[1]					Treatment End
Treatment Day	**57**	**78**	**99**	**120**	**141**	**150**
Scheduling Window (days)[2]	**-3/+7**	**-3/+7**	**-3/+7**	**-3/+7**	**-3/+7**	**-7/+14**
Laboratory Procedures/Assessments (local laboratory testing):						
CBC with differential	**x**	**x**	**x**	**x**	**x**	**x**
Serum Chemistry Panel[5]	**x**	**x**	**x**	**x**	**x**	**x**
Uric Acid	**x**	**x**	**x**	**x**	**x**	**x**
Magnesium	**x**					
Urinalysis	**x**	**x**	**x**	**x**	**x**	**x**
T3, FT4, TSH				**x**		**x**
Imaging						
Tumor Imaging (CT neck[12], PET[14])						**x**
Correlative Study Procedures						
Blood for correlative studies[10]		**x**		**x**		**x**
Salvage surgery collection[13]						**x**
Patient Reported Outcomes (PRO)						
FACT H&N[11]		**x**				**x**

6.3 Follow-up

	Months Following Study Treatment End (after day 150 imaging)								
Follow-up Month	**Follow up visit 1** (90 days from Day 150)	**Follow up visit 2** (90 days from FU-V1)	**Follow up visit 3** (180 days from FU-V2)	**Follow up visit 4** (180 days from FU-V3)	**Follow up visit 5** (180 days from FU-V4)	**Follow up visit 6** (352 days from FU-V5)	**Follow up visit 7** (352 days from FU-V6)	**Follow up visit 8** (352 days from FU-V7)	**Study End**
Scheduling Window	**+/- 14 days**	**+/- 30 days**	**+/- 30 days**	**+/- 30 days**	**+/- 30 days**	**+/- 30 days**	**+/- 30 days**	**+/- 30 days**	
Administrative Procedures									
Subsequent antineoplastic therapy status	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	
Survival Status[16]	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	
Clinical Procedures and Assessments									
Adverse Events[20]	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	
Directed Physical Exam	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	
Vitals and Weight (optional)	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	
ECOG PS(optional)	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	

	Months Following Study Treatment End (after day 150 imaging)								
Follow-up Month	**Follow up visit 1** (90 days from Day 150)	**Follow up visit 2** (90 days from FU-V1)	**Follow up visit 3** (180 days from FU-V2)	**Follow up visit 4** (180 days from FU-V3)	**Follow up visit 5** (180 days from FU-V4)	**Follow up visit 6** (352 days from FU-V5)	**Follow up visit 7** (352 days from FU-V6)	**Follow up visit 8** (352 days from FU-V7)	**Study End**
Scheduling Window	**+/- 14 days**	**+/- 30 days**	**+/- 30 days**	**+/- 30 days**	**+/- 30 days**	**+/- 30 days**	**+/- 30 days**	**+/- 30 days**	
Laboratory Procedures/Assessments (local laboratory testing):									
CBC with differential	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	
Serum Chemistry Panel[5]	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	
T3, FT4, TSH		**x**	**x**	**x**	**x**	**x**	**x**	**x**	
Imaging									
Tumor Imaging (CT neck)	**x**	**x**	**x**		**x**	**x**	**x**	**x**	
Correlative Study Procedures									
Blood for correlative studies[10]			**x**						
Patient Reported Outcomes (PRO)									
FACT H&N[11]			**x**		**x**				

1. Treatment day 1 coincides with the first day of radiation therapy. Any treatment days before will be denoted with a preceding (-) symbol.
2. The window for each visit is outlined as above. If a treatment is delayed, the following treatment must occur with the same delay. Additional treatment delay can occur with the specified scheduling window. If treatment is delayed beyond that window, treatment for that scheduled course must be held. Treatment can be resumed for the next scheduled treatment day.
3. Radiation occurs continuously throughout therapy until the total of 35 fractions has been completed. Therefore, the dates listed may not always have radiation treatment on that date. All radiation should be completed by day 52.
4. For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If urine pregnancy tests cannot be confirmed as negative, a serum pregnancy test, performed by the local lab, will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
5. The serum chemistry panel includes tests listed in Section 7.1.3, Table 5(Albumin, AST, ALT, Alkaline phosphatase, Total Bilirubin (and direct bilirubin if elevated), Total Protein, CO_2, Calcium, Chloride, Glucose, Potassium, Sodium, Creatinine, and BUN).
6. p16 immunohistochemistry status is required on all patients. This can be performed by the local laboratory sites. High risk HPV DNA testing at an outside lab can be performed if p16 staining is indeterminate or not able to be obtained. See section 5.1.2 for details.
7. Tumor tissue for biomarker analysis from an archival tissue sample or fresh biopsy must be provided for enrollment. Detailed instructions for tissue collection, processing and shipment are included in the procedures manual.
10. Blood for correlative flow cytometry studies will be drawn throughout treatment. On days with corresponding treatment, this should be drawn within 24 hours prior to treatment with pembrolizumab or chemotherapy. Procedures for sample collection, processing, and shipment are included in the procedures manual.
11. Patient reported outcomes (PRO) will be assessed using the FACT H&N form (see Appendix 11.8). PRO forms must be completed on paper or electronically by subjects prior to all other study procedures for that date. Patients who go off-treatment but continue follow up should be encouraged to complete PRO at the times outlined in the calendar.
12. Tumor imaging will be completed at baseline and after treatment has finished, on approximately day 150-157. Baseline imaging must be completed within 42 days of enrollment. Required imaging for the study protocol is diagnostic quality imaging of the neck. Additional imaging techniques can be utilized (i.e. MRI, FDG-PET, etc.), but are not required for study procedures.
13. Patients with residual disease (SD, PR, or PD) on post-treatment imaging will undergo salvage surgical resection (at the discretion of the surgeon) if their disease is felt curable with salvage surgery. Additionally, patients with a CR and clinical suspicion for viable residual disease will be offered salvage surgery. Following pathology analysis, salvage surgical tissue will be sent for correlative studies. Detailed instructions for tissue collection, processing, and shipment are included in the procedures manual.
14. PET imaging at baseline and treatment end is not required for the study, but is allowed for use to determine complete response rate when tumor response on standard imaging cannot confirm CR based on RECIST 1.1. Please see sections 7.1.2.6.2 and 7.1.2.6.3 for details.
15. Screening labs completed within 7 days (168 hours) of treatment initiation (day -7) will not need to be repeated.
16. Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the Survival Follow-Up Phase. These subjects will be followed every 6 months to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.
17. If a subject discontinues pembrolizumab, return visit timing is left to treating physician discretion until day 150 although it is highly recommended that the subject return for Day 78, 120, and 150 so research specimens and QOL can be collected.
18. Minimum interval between pembrolizumab doses is 14 days.
19. Vital signs and weight do not need to occur on the same day as the visit but need to be completed within the window and prior to the next treatment.
20. Once a subject transitions to follow-up all documented AEs will be followed until resolution or to a new baseline as determined by the treating investigator. Only new AEs that could be considered an ECI or irAR will be documented and followed while in follow-up.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The informed consent will adhere to IRB/ERC requirements, applicable laws, regulations, and Sanford Research requirements.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered clinically significant by the Investigator. Details regarding the disease for

which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

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

7.1.1.4.2 Concomitant Medications

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

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

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

7.1.1.5.2 Prior Treatment Details

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

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

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

7.1.1.6 Assignment of Screening Number

Consented subjects will be assigned a screening number. Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1.

7.1.1.7 **Assignment of Study Subject Number**

Subjects will be assigned a subject study number at enrollment. This number will be unique to this subject.

7.1.1.8 **Trial Compliance (Medication/Diet/Activity/Other)**

Interruptions from the protocol specified treatment plan for >1 week require consultation with the principal investigator. Written documentation of the collaborative decision is required.

Missed doses of the study drug, pembrolizumab, will be monitored and tracked. This will be analyzed as part of the safety and tolerability portion of the analysis.

7.1.2 **Clinical Procedures/Assessments**

7.1.2.1 **Adverse Event (AE) Monitoring**

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study according to NCI CTCAE Version 4.0 (see Section 11.2). Toxicities will be characterized in terms regarding seriousness, causality/attribution, toxicity grading, and action taken with regard to trial treatment.

AEs should be assessed up to 30 days following cessation of treatment and followed for 90 days for SAEs, even if the patient transitions to follow-up during this time. Once a subject transitions to follow-up all documented AEs will be followed until resolution or to a new baseline as determined by the treating investigator. Only new AEs that could be considered an ECI or irAR will be documented and followed while in follow-up.

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

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

7.1.2.2 **Full Physical Exam**

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

7.1.2.3 **Directed Physical Exam**

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

7.1.2.4 **Vital Signs**

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 6.0). Vital signs after Day 150 will be at the discretion of the treating investigator. Vital signs should include temperature, pulse, weight and blood pressure. Height will be measured at screening only.

7.1.2.5 **Eastern Cooperative Oncology Group (ECOG) Performance Scale**

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

7.1.2.6 **Tumor Imaging and Assessment of Disease**

7.1.2.6.1 Baseline Tumor Imaging

Initial tumor imaging must be performed within 42 days prior to enrollment. Baseline imaging does not need to have a centralized study review to determine subject eligibility. The baseline imaging scan should be reviewed by each individual site prior to enrollment to confirm measurable disease.

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

The only required imaging modality for the study is a diagnostic quality CT scan of the neck. This should be adequate to fully include the primary tumor and involved locoregional disease. Additional imaging is allowed, but not required for the study. This includes, but is not limited to CT imaging of the head, chest, abdomen, and pelvis, MRI imaging, and FDG-PET imaging.

7.1.2.6.2 Tumor Imaging During Trial

The first imaging assessment should be performed at approximately **100 days after completion of radiation therapy**. For the purposes of this study, this is considered the "treatment end" imaging study. This will be approximately day 150 from the first dose of radiation. Due to treatment variations and delays, this may be delayed by up to 14 days.

Follow-up imaging will occur at scheduled intervals outlined on the Flow Chart. At 1 year following completion of the study treatment PET/CT imaging is not required, but is suggested

and is allowed so long as diagnostic quality CT images are included. Diagnostic quality imaging of the primary tumor site (CT scan of the neck) should be performed annually thereafter for up to 5 years. Images will be reviewed by the central radiologist at the end of the study to confirm disease response for purposes of study evaluation.

Additional imaging should be performed per clinical guidelines and is not required the study. Patients with clinical signs and symptoms of progression should have follow-up imaging as deemed clinically necessary. If this occurs during the study period, it should be reported to the study.

During the follow up period, if an instance occurs where the participants insurance will not approve a diagnostic CT scan a clinical evaluation will be used. No protocol deviation is needed but the insurance denial must be documented on the tumor assessment source documents.

7.1.2.6.3 Assessment of Disease – RECIST 1.1, irRECIST 1.1, PET Response, Salvage Surgery

7.1.2.6.3.1 RECIST 1.1

RECIST 1.1 will be applied by the individual sites for assessment of tumor response. Sites should also assess tumor response and progression per modified RECIST 1.1 and this data will be collected in the clinical database. Site assessment of tumor response and progression will be used for all patient decision making in the trial. See Section 11.3 and 11.4.

7.1.2.6.3.2 irRECIST 1.1

irRECIST 1.1 will not be used in this study. Any patient with documented progression, partial response, or stable disease on post-treatment imaging will undergo salvage surgical procedures to confirm pathologic response (see Section 7.1.2.7.3.3).

7.1.2.6.3.3 PET Response (Hopkins Criteria)

Hopkins Criteria will be used to assess PET response when PET imaging is utilized. This is outlined in section 11.5. PET is not required, but is allowable to assist in determine the primary efficacy outcome when RECIST 1.1 data is considered not clinically representative of response. Patients without a RECIST 1.1 CR, but with a Hopkins Criteria negative predictive value (NPV) (See section 11.5) can forgo salvage surgery and be considered as having a CR in terms of the primary efficacy measure.

7.1.2.6.3.4 Salvage Surgery

Patients with residual disease considered resectable after all their planned therapy is completed may undergo a salvage surgical procedure, if that procedure is conceived as potentially curative.

PET imaging can be used to guide post treatment surgical need. The preference of the study would be to recommend no further therapy for any PET tumor avidity (CMR). However, this is not a requirement and will be left up to the discretion of the treating surgical oncologist.

Patients achieving a complete response who had advanced (N2 or greater) neck disease at presentation should be considered for an elective neck dissection after completion of all of their planned therapy if the post therapy imaging or clinical exam indicates persistent disease, despite RECIST 1.1 response. The nature of the neck dissection will be at the discretion of the treating head and neck surgeon.

Pathologic response to therapy will be evaluated following surgery. Pathological complete response (pCR) is defined as the absence of residual invasive and in situ cancer on hematoxylin and eosin evaluation of the completely resected sites of residual disease. Subjects who have a pathologic CR, but do not have a RECIST 1.1 CR will be included in the final efficacy analysis. This analysis will include the composite outcome of patients with RECIST 1.1 CR, Hopkins Criteria NPV (see section 11.5), and pathologic CR.

Patients who show signs of clear, clinical progression prior to the treatment end imaging may be considered for surgery. This will be at the discretion of the treating providers, including the surgeon, medical oncologist, and radiation oncologist. Patients who undergo surgery will be determined to have PD in terms of analysis of the primary endpoint.

7.1.2.7 **Tumor Tissue Collection and Correlative Studies Blood Sampling**

7.1.2.7.1 Tumor Tissue Collection

All subjects will submit either a “recently obtained” core or excisional biopsy (fine needle aspirate not adequate) to a central lab for characterization of PD -L1 status, performed retrospectively. A “recently obtained” sample may be obtained up to 60 days prior to enrollment. Tissue beyond the 60-day window may be considered with principal investigator approval as long as no intervening systemic therapy has been administered. Subjects for whom recently obtained samples cannot be obtained (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the principal investigator. Formalin fixed paraffin embedded (FFPE) are allowable.

Post-treatment biopsy of the primary site if tumor persists and salvage neck dissection specimens will be analyzed for tumor PD-L1 expression and tumor infiltrating immune cells.

For correlative genomic analysis, an additional portion of the pre-treatment core or excisional biopsy will be used for analysis. If fresh frozen tissue is available, RNA profiling studies may

be performed, but this is not a requirement for the study. Correlative circulating tumor DNA may be also be analyzed. This will be collected in addition to other correlative blood sampling. Details of collection and appropriate specimens are outlined in the procedures manual.
Detailed instructions for tissue collection and appropriate specimens are provided in the Procedures Manual.

7.1.2.7.2 Correlative Blood Sampling

Correlative blood sampling for biomarkers of immune response will be collected at key time points during the study. These are not required for all subjects, but are strongly recommended. Timing for correlative blood sampling is outlined in section 6 – Trial Flow Chart. To summarize:

Blood sampling for flow cytometry or functional immune cell analysis will be used to analyze peripheral blood immunocyte populations will occur on day-7, day 15, day 36, day 78, day 120, treatment end (day 150-157), and at 12 months treatment.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5.

Table 5 Laboratory Tests

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

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

Screening laboratory tests may be done up to 10 days prior to start of treatment but if done less than 7 days (168 hours) prior to the first dose of treatment on Day -7, they will not need to be repeated. After Day -7, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.3.1 **Tissue Collection and Evaluation**

7.1.3.1.1Tumor Collection for p16, PD-L1, and Genomic Analysis

All subjects will have p16 immunohistochemical (IHC) staining (high risk HPV DNA testing may be used as outlined in section 5.1.2) done per institutional standard procedures prior to treatment.

All subjects will submit a recently obtained core or excisional biopsy (within 60 days from enrollment). Fine-needle aspirates (FNAs) are not adequate. Characterization of PD-L1 will be performed using IHC. Detailed instructions for processing of specimens and testing are outlined in the procedures manual and statistical analysis plan (SAP).

For correlative genomic studies, tumor tissue blocks will be micro-dissected and Tumor DNA and RNA will be immediately processed and stored. Detailed instructions for processing of tumor specimens and testing are outlined in the SAP.

For infiltrating immunocyte analysis, tumor tissue blocks will be stored in the Sanford or similar UCSD facility and testing will be completed at a later date. Detailed instructions for processing of tumor specimens are outlined in the SAP.

7.1.4 **Other Procedures**

7.1.4.1 **Withdrawal/Discontinuation**

When a subject discontinues/withdraws prior to active trial completion, the subject will need to sign a withdrawal consent. If the subject becomes cognitively impaired while on this study the subject and/or their Legal Representative will have the opportunity to sign a withdrawal consent. All applicable activities scheduled for the final trial visit should be performed at the time of discontinuation/withdrawal. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. After discontinuing treatment following completion, subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

Subjects will have the option to withdraw from the study completely or partially which will allow following for progression/survival.

7.1.4.2 **Blinding/Unblinding**

There is no blinding for this trial.

7.1.5 **Visit Requirements**

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

7.1.5.1 **Screening**

7.1.5.1.1 Screening Period

Approximately 28 days prior to treatment (day-36), potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time

frame. Screening procedures are to be completed within 28 days prior to the first dose of trial treatment except for the following:

- Laboratory tests and ECOG performance status are to be performed within 14 days prior to the first dose of trial treatment.
- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first dose of trial treatment.
- Biopsy collections may be collected up to 60 days prior to enrollment as presented in Sections 5.1.1 and 6.1.

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7.1.5.2 **Treatment Period**

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

7.1.5.3 **Post-Treatment Visits**

Subjects will be followed for up to 5-years following treatment completion. The Trial Flow Chart – Section 6 outlines visit requirements and study procedures required at these visits. Further details are outlined in the subsections below.

7.1.5.4 **Safety Follow-Up Visit**

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first, for those subjects who do not complete active treatment. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1, return to baseline, or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

7.1.5.5 **Follow-up Visits**

Follow-up visits for subjects who complete study treatment are outlined in the Trial Flow Chart – section 6.

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, or end of study. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

7.1.5.6 **Survival Follow-up**

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the Survival Follow-Up Phase. These subjects will be followed every 6 months to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.2 **Assessing and Recording Adverse Events**

An adverse event is defined as any untoward medical occurrence in a patient that received a pharmaceutical product during the course of the study, whether or not they are considered related to the product. This includes changes in laboratory parameters. Any medical condition that is present before the subject starts study medication and does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study it should be recorded as an AE.

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

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

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

All acute adverse events will be recorded from the time the subject receives the first dose of treatment through 30 days following cessation of treatment. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1.

7.2.1 **Definition of an Overdose for This Protocol and Reporting of Overdose to the Sanford Research and to Merck**

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

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

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

Overdoses of radiation and cisplatin will be in accordance with the respective local product label and standard procedures.
All reports of overdose with and without an adverse event must be reported within 24 hours to Sanford Research and within 2 working days' hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.2 **Reporting of Pregnancy and Lactation to Sanford Research and to Merck**

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to Sanford Research and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.3 **Immediate Reporting of Adverse Events to Sanford Research and to Merck**

7.2.3.1 **Serious Adverse Events**

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

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

Refer to Table 6 for additional details regarding each of the above criteria.

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

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

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

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the principal investigator and to Merck.

SAE reports and any other relevant safety information are to be forwarded to Sanford Research via email at SH-MISP@sanfordhealth.org or fax (1-605-312-3321) and to the Merck Global Safety facsimile number: +1-215-993-1220.

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

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

7.2.3.2 Events of Clinical Interest

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

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

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the

upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

1. Additional adverse events:

   A separate guidance document has been provided entitled "Event of Clinical Interest Guidance Document". This document provides guidance regarding identification, evaluation and management of ECIs and irAEs.

   ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported within 24 hours to Sanford Research **via email at SH-MISP@sanfordhealth.org or fax (1-605-312-3321** and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220), regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

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

7.2.4 **Evaluating Adverse Events**

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

7.2.4.1 **Table 6 Evaluating Adverse Events**

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Merck product to be discontinued?	
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality/attribution noted on the AE form, ensures that a medically qualified assessment of causality/attribution was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

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

7.2.5 Sanford Research Responsibility for Reporting Adverse Events

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

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Study Oversight Committee

The Study Oversight Committee (SOC) comprises members of Study Team and is led by the Principal Investigator. The SOC will receive and follow up on any recommendations made by the Data Safety and Monitoring Board (DSMB) regarding the trial.

7.3.2 Data Safety and Monitoring Board (DSMB)

An independent DSMB will be established with experienced members, none of whom are participating as study investigators, to monitor and evaluate the safety of subjects, to maintain oversight of study data and to monitor progress of the study. The board will meet at according to the DSMB Charter approved at the beginning of the trial. The DSMB may also meet at unscheduled times according to clinical necessity. All SAEs will be reported to the DSMB as soon as possible after learning of the event.

The DSMB will make recommendations to the SOC regarding steps to ensure subject safety and the continued ethical integrity of the trial. The DSMB will review interim study results and consider the overall risk and benefit to trial participants. They will recommend to the SOC whether the trial should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members of the DSMB; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DSMB reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DSMB.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

A brief summary of the statistical analysis plan (SAP) is outlined in the table below. A more detailed description of statistical plan begins at section 8.2 and continues in the SAP

Study Design Overview	Phase IB study of Pembrolizumab in combination with chemoradiotherapy (CRT) for locally advanced squamous cell carcinoma of the head and neck (SCCHN)
Treatment Assignment.	Treatment assignment is open label
Analysis Populations	Efficacy: Full Analysis Set (FAS) Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	1) Safety and Tolerability 2) Efficacy: Complete Response (CR) Rate at treatment end.
Statistical Methods for Key Efficacy Analyses	The key efficacy analysis is estimation of the treatment end CR rate using Exact method based on binomial distribution. There is no statistical hypothesis.
Statistical Methods for Key Safety Analyses	Count and percentage of AE will be provided. Fisher's exact test will be used to compare the proportions.
Interim Analyses	Interim efficacy analysis will be performed when 27 subjects have enrolled in this study and are evaluable for response (day 150). Efficacy results will be reviewed by the DSMB.
Multiplicity	Not included in this study.
Sample Size and Power	Sample size is based off the efficacy endpoint. It is estimated that57 evaluable patients, will be sufficient to determine the efficacy endpoint with a power = 0.8 and one-sided alpha = .05.

8.2 Statistical Analysis Plan (SAP)

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. See the statistical analysis plan (SAP) for more information.

8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

8.4 **Analysis Endpoints**

8.4.1 **Efficacy Endpoints**

Radiographic Complete response (rCR) rate: proportion of subjects in the analysis population who have a complete response on RECIST 1.1 imaging at treatment end.

PET NPV rate: proportion of subjects in the analysis population who are considered to have NPV based on Hopkins Criteria scoring at treatment end.

Pathologic complete response (pCR) rate: proportion of subjects in the analysis population who have stable disease (SD) or partial response (PR) on RECIST 1.1 imaging at treatment end, who undergo salvage surgical resection and have a complete response determined on histologic evaluation.

Overall Complete Response (CR) rate: this is a composite proportion of subjects in the analysis population with a rCR, PET NPV , and pCR. This is the primary measure of efficacy for the study.

Overall Response Rate (ORR): proportion of subjects in the analysis population who have complete response (CR) or partial response (PR) based on RECIST 1.1 imaging at treatment end.

Progression-Free Survival (PFS): time from Day -7 treatment administration to the first documented disease progression or death.

Overall Survival (OS): time from Day -7 treatment administration to death due to any cause.

Locoregional Control (LRC): time from day -7 treatment to date of local or regional relapse within the primary radiation treatment field (relapse in the head or neck region, excluding CNS recurrence).

Rate of Distant Metastases (DM): proportion of subjects in the analysis population who develop distant recurrence, as defined by recurrence outside of the primary radiation treatment field (head and neck region).

8.4.2 **Safety Endpoints**

The primary safety objective of this trial is to characterize the safety and tolerability of pembrolizumab in subjects with head and neck cancer. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE Version 4.0 criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab, including serious adverse events (SAEs) and events of clinical interest (ECIs).

Safety will be assessed by reported adverse experiences using CTCAE, Version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific immune-related adverse events (irAEs) will be collected and designated as immune-related events of clinical interest (ECIs) as described in Section 7.2.3.2.

Consider referring to Section 4.2.3 for the initial description of safety measures.

8.4.2.1 **Analysis Populations**

8.4.2.2 **Efficacy Analysis Populations**

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all subjects who:

- Receive at least one dose of study treatment,
- Complete the treatment end imaging study

A supportive analysis using the All Patients as Treated (APaT) population, defined as all enrolled subjects who receive at least one dose of study medication, will be performed for the primary efficacy endpoint(s). Supportive analyses in the FAS population using the site radiology assessment will require baseline scan with measureable disease per RECIST 1.1 using site radiology assessment.

Patients who undergo surgical resection prior to treatment end imaging will be included in the efficacy analysis. These patients will be determined as having PD.

Details on the approach to handling missing data are provided in Section 8.6 Statistical Methods.

8.4.2.3 **Safety Analysis Populations**

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.4.3 **Statistical Methods**

8.4.3.1 **Statistical Methods for Efficacy Analyses**

The efficacy endpoints, analysis population, and statistical methods (including missing data handling) that will be employed for the efficacy analyses are presented in Table 7.
The primary endpoint is the total CR rate (composite outcome of rCR, PET NPV, and pCR) on all subjects. We have designed the study to test the hypothesis that the CR rate will be greater than 40.2% assuming a rate of 60.4%. To test this, we will use a one sample, one-sided asymptotic equality test with the null hypothesis that the total CR rate will be 40.2%. This test will result in a p-value greater than 0.05 if fewer than 21 patients respond to treatment. Secondary endpoints will include rCR, pCR, PET NPV, PFS, OS, LRC, and DM rates. For the secondary endpoints, we will only estimate confidence intervals to understand the possible range of values rather than doing formal hypothesis testing. Survival curves for PFS and OS will be constructed using the Kaplan-Meier method and 1 and 2-year survival estimates will be calculated.

8.4.3.2 **Table 7: Statistical Methods for Key Efficacy Endpoints**

Endpoint	Statistical Method	Analysis Population	Missing data approach
rCR Rate	Exact binomial method: Clopper-Pearson 95% confidence interval	FAS	Subjects with missing data are considered non-responders
pCR Rate	Exact binomial method: Clopper-Pearson 95% confidence interval	FAS[1]	Subjects with missing data are considered non-responders
CR Rate	One sample, one-sided asymptotic binomial test	FAS	Subjects with missing data are considered non-responders
Objective Response Rate (CR + PR)	Exact binomial method: Clopper-Pearson 95% confidence interval	FAS	Subjects with missing data are considered non-responders
PFS (RECIST 1.1) by independent radiology review	Summary statistics using Kaplan-Meier method	ASaT	Censored at last assessment date
OS	Summary statistics using Kaplan-Meier method	ASaT	Censored at last assessment date
LRC rate	Exact binomial method: Clopper-Pearson 95% confidence interval	FAS	Subjects with missing data are considered as disease not under control
DM rate	Exact binomial method: Clopper-Pearson 95% confidence interval	FAS	Subjects with missing data are considered as disease not under control

Patient Reported Outcomes (PRO)	Linear mixed model to compare with historical controls over time.	ASaT	Missing data will not be included
1 – only those who undergo salvage surgery			

8.4.4 **Statistical Methods for Safety Analyses**

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events (AEs), laboratory tests, and vital signs. Count and percentage of AE will be provided. Clopper-Pearson 95% confidence interval for the proportion of AE of clinical interest will be estimated using exact method based on binomial distribution. AE rates will be compared, using a Fisher's exact test to compare the proportions. This will also be compared to historical data from patients treated on a similar clinical trial using high-dose bolus cisplatin in combination with radiation which was recently performed at the primary study site (Sanford Cancer Center, Sioux Falls and Sanford Roger Maris Cancer Center, Fargo).

8.4.5 **Summaries of Baseline Characteristics, and Demographics**

The number and percentage of subjects screened, enrolled, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

8.4.6 **Patient Reported Outcomes (PROs) Evaluation**

The FACT-H&N questionnaire will be will be used to assess HRQOL (See 11.7). This questionnaire combines 27 questions from the FACT-G scale with 12 disease specific questions for head and neck cancer. The FACT-H&N can be subdivided into five subscales which include the four subscales of the FACT-G (physical well-being, social/family well-being, emotional well-being, and functional well-being) and the Head and Neck Cancer Subscale. This questionnaire is widely used in head and neck cancer patients and has been validated within this population [22].

The FACT-H&N questionnaire will be requested at defined time points; at baseline, end of treatment, 6 months, 1 year, and 1 years post treatment. The initial questionnaire must be filled out prior to any treatment.

Statistical analysis of HRQOL will involve global HRQOL as well as each of the five domains in the FACT-H&N questionnaire. Longitudinal analysis will be conducted using a linear mixed model to compare the overall score and subscales scores between the patients in this trial and historical controls.

8.4.7 **Interim Analyses**

A formal interim efficacy analysis will occur after 27 patients have enrolled in the study. This analysis will be reviewed by the DSMB to determine if the study should continue to accrue to a total of 39 evaluable patients. A non-formal safety analysis will occur after approximately 8 patients have completed the study treatment. This analysis will not involve stopping the study. The DSMB will meet and review toxicities at that time point. If it is felt there is risk beyond what is to be expected for standard CRT, the DSMB will determine if the study should be stopped and if a formal safety analysis is warranted.

8.4.7.1 **Interim Efficacy Analysis**

An interim analysis will also occur to evaluate efficacy. The interim analysis will occur after 27 patients are accrued to the study and have treatment end response assessments completed (imaging and if applicable, salvage surgical resection). This will occur at approximately 9 months after study initiation. In terms of efficacy, futility will be determined if 13 or fewer CRs (rCR +pCR) are seen in the 27 patients. If futility is not determined, the study will continue to accrue to final total of 34 HPV + patients and 23 HPV - patients who are evaluable for treatment response. This will be presented to and evaluated by the DSMB.

8.4.7.2 **Multiplicity**

No multiplicity adjustment is planned.

8.4.7.3 **Sample Size and Power Calculations**

Sample size for this study will be powered based on the co-primary outcome of efficacy. Efficacy will be defined by the rCR rate at the treatment end imaging evaluation. The rCR rate will be defined by RECIST 1.1 criteria. Based on the Intergroup Trial evaluating the gold standard of high-dose bolus cisplatin 100 mg/m2 given on days 1, 22, and 43 of radiation at 70 cGy, the complete response rate was 40.2% [10]. This study included both HPV+ and HPV- patients with unresectable disease and did not differentiate response based on HPV status. Extrapolating on our data from the animal model, we anticipate at least a 50% improvement in this CR rate. Therefore, we estimated a CR rate of 60.4% with this study regimen in all-comers.

For the initial sample size calculation, Simon's two-stage design with the Minimax approach was utilized. The null hypothesis that the true response rate is 0.402 will be tested against a one-sided alternative. In the first stage, 27 patients were to be accrued. If there are 13 or fewer CRs in these 27 patients, the study will be stopped. Otherwise, 12 additional patients will be accrued for a total of 39. The null hypothesis will be rejected if 21 or more CRs are observed in 39 patients. This design yielded a type I error rate of 0.05 and power of 0.80 when the true CR rate is 0.604.

At the time of interim analysis, 27 patients are enrolled in the study. During this analysis, an internal analysis of a similar study (NCT01386632) using standard of care high-dose cisplatin

(100 mg/m2 on days 1, 22, and 43) in a similar cohort of patients was performed. Distinct differences in response were seen in the HPV+ and HPV- groups, which mirror efficacy findings in similar studies. This analysis has revealed that 20 of 27 (74%) of evaluable patients with HPV positive disease achieved a CR (based on 3-month post-radiation CT and/or PET or subsequent salvage surgery).

Based on this new data, we have reassessed our power calculations for our HPV positive cohort, With this novel combination therapy we estimate that an improvement in efficacy of >20% to a CR rate of 90% would warrant future study of this regimen in HPV positive disease. Therefore, using a one-arm binomial design the null hypothesis that the true response rate is 74% will be tested against a one-sided alternative. The null hypothesis will be rejected if 31 or more CRs are observed in 34 patients. This design yields a type I error rate of 0.05 and power of 80% when the true response rate is 90%.

Reviewing the same data, the HPV negative cohort had 6 of 12 (50%) evaluable patients achieving a CR (based on 3-month post-radiation CT and/or PET or subsequent salvage surgery). Therefore, reassessing our power calculations for the HPV negative cohort in the proposed expansion cohort, we estimate a CR rate of 75% (50% improvement from the standard of care) with the study regimen would warrant future study of this regimen in HPV negative disease. Therefore, using a one-arm binomial sample size, the null hypothesis with a true response rate of 50% will be tested against a one-sided alternative. The null hypothesis will be rejected if 18 or more responses are observed in 23 patients. This design yields a type I error rate of 0.05 and power of 80% when the true response rate is 75%.

At the time of the interim analysis, 20 patients with HPV + disease are enrolled and 7 patients with HPV – disease are enrolled. Based on this reanalysis of sample size and power calculations, an additional 14 HPV positive patients and 16 HPV negative patients would need to be enrolled after the interim analysis.

8.4.7.4 **Subgroup Analyses and Effect of Baseline Factors**

All efficacy endpoints CR rate, ORR, PFS, OS, LRC rate, and DM rate will be evaluated and compared based on:

- HPV-positive and HPV-negative status
- PD-L1 positive and PD-L1 negative status
- Additional correlative studies as pertinent
- ECOG PS 0 or 1
- Key demographic variables (i.e. age, sex, etc.) as deemed appropriate

Differences in subgroups will be evaluated using appropriate statistical techniques adjusting for key demographic variables. Models will include logistic regression and proportional hazards regression.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies are as summarized in Table 8.

Table 8 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/ 4mL[1]	Solution for Injection

1-Provided by Merck

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

The Pembrolizumab product that will be supplied for this trial is not an approved US commercial product at this time. It is, however, filed to the Merck IND along with data supporting a claim of analytical comparability of this product to all other pembrolizumab products being used in the clinic, some of which have been approved by the US FDA for commercial use.

This trial is open-label; therefore, the subject, the trial site personnel, Sanford Research and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text.

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

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

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all sub-investigators and trial site personnel,

may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

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

Consistent with the purposes described above, this information may be transmitted to Sanford Research, and subsidiaries, affiliates and agents of Sanford Research and Merck.

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

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

10.1.4 **Confidentiality of IRB/IEC Information**

Sanford Research is required to record the name and address of each IRB/IEC member that reviews and approves this trial. Sanford Research is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 **Compliance with Financial Disclosure Requirements**

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

The investigator/sub investigator(s) agree, if requested by Sanford Research in accordance with 21CFR Part 54, to provide his/her financial interests in and/or arrangements with Sanford Research to allow for the submission of complete and accurate certification and disclosure statements. The investigator/sub investigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by Sanford Research or through a secure password-protected electronic portal provided by Sanford Research. The investigator/subinvestigator(s) also consent to the transmission of this information to Sanford Research for these purposes.

10.3 **Compliance with Law, Audit and Debarment**

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

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

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

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

Trial documentation will be promptly and fully disclosed to Sanford Research by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of Sanford Research or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by Sanford Research as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. Sanford Research will determine the minimum retention period and notify the investigator when documents may be destroyed Sanford Research also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by Sanford Research prior to destroying trial and/or subject files. ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform Sanford Research of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on Sanford Research's trials. The investigator will immediately disclose in writing to Sanford Research if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

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

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), Sanford Research is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

10.5 Quality Management System

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

10.6 **Data Management**

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature.
Detailed information regarding Data Management procedures for this protocol will be provided separately.

11.0 APPENDICES

11.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

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

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

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

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

Baseline Eligibility

Measurable Disease:	**Tumor lesions:** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:: o 10 mm by CT by computerized tomography (CT scan slice thickness no greater than 5 mm). o 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable). o 20 mm by chest x-ray. **Skin lesions:** Documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. **Malignant lymph nodes:** To be considered pathologically enlarged and measurable, a lymph node must be $\geq$ 15mm in short axis when assessed by CT scan.. At baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable Disease:	All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with $\geq$ 10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, and lymphangitic involvement of skin or lung, abdominal masses, abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
Target Lesions:	The most reproducible measurable lesions, up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), should be representative of all involved organs, and, in addition, should be those that lend themselves to reproducible repeated measurements. Pathological nodes which are defined as measurable and that may be identified as target lesions must meet the criterion of a short axis of ≥ 15mm. All target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor response.

Non-Target Lesions: All other lesions (or sites of disease) are identified as non-target lesions (chosen based on their representativeness of involved organs and the ability to be reproduced in repeated measurements) and should be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up. Lymph nodes with short axis ≥ 10mm but < 15mm should be considered non-target lesions. Nodes that have a short axis < 10mm are considered non-pathological and are not recorded or followed.

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10mm. Tumor marker results must have normalized

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest (nadir) sum of diameters since the treatment started.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest (nadir) sum since the treatment started, or the appearance of one or more new lesions. Requires not only 20% increase, but absolute increase of a minimum of 5 mm over sum.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor markers. All lymph nodes must be non-pathological in size (<10 mm short axis).

Stable Disease (SD): Persistence of one or more non-target lesions and/or persistence 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. When the patient also has measurable disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

Evaluation of Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall response	**CR:** disappearance of all target and non-target lesions, normalization of tumor marker level, and reduction in pathological lymph nodes short axis to <10 mm. **PR:** 30% decrease in the sum of diameters of the target lesions. **PD:** 20% increase in the sum of diameters of the target lesions.
CR	CR	No	CR	
CR	Non-CR / non-PD	No	PR	
CR	NE	No	PR	
PR	Non-PD or NE	No	PR	
SD	Non-PD or NE	No	SD	
Not all evaluated	Non-PD	No	NE	
PD	Any	Yes or No	PD	
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

When nodal disease is included in the sum of target lesions, and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate

progression, should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of ‘zero’ on the case report form (CRF).
* As published in the European Journal of Cancer:

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

11.4 **Modified RECIST 1.1**

Modified RECIST 1.1 is RECIST 1.1 adapted as follows to account for the unique tumor response seen in this class of therapeutics (refer to Section 4.2.3.1).

If radiologic imaging shows PD, tumor assessment may be repeated >=4 weeks later at the site in order to confirm PD with the option of continuing treatment for clinically stable subjects as discussed below. Clinically stable is defined by the following criteria:

Absence of signs and symptoms indicating disease progression
•No decline in ECOG performance status
•Absence of rapid progression of disease
•Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

Imaging and Treatment after 1st radiologic evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
1st radiologic evidence of PD	Repeat imaging at >=4 weeks at site to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory scan by site	Repeat imaging at >=4 weeks at site to confirm PD per physician discretion only	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment	No additional imaging required	N/A
Repeat scan shows SD, PR, or CR	Continue regularly scheduled imaging assessments	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion

In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation. If radiologic progression is confirmed (by subsequent scan) then the subject will be discontinued from

trial treatment.

If radiologic progression is not confirmed, then the subject should resume/continue trial treatment and have their next scan at the regularly scheduled interval. Subjects who obtain a confirmation scan at 4 weeks do not need to undergo the next scheduled imaging assessment if it is due < 4 weeks later. Imaging may be performed at the next scheduled imaging time point if the subject remains clinically stable.

NOTE: If a subject with confirmed radiographic progression (i.e. 2 scans at least 28 days apart demonstrating progressive disease) is clinically stable or clinically improved, and there is no further increase in the tumor dimensions at the confirmatory scan, an exception may be considered to continue treatment upon consultation with the Sponsor.

Imaging during the follow-up period is to be repeated every 6 weeks (± 7 days) for the first year patients are on study and then every 9 weeks (± 7 days) after 1 year for subjects who discontinue trial treatment for reasons other than disease progression. Follow-up scans should be continued until the subject experiences confirmed disease progression or starts a new antineoplastic therapy.

11.5 **Hopkins Criteria for PET Response Evaluation in Head and Neck Cancer**

Post-treatment FDG PET/CT imaging will be utilized as part of the response criteria, based on clinical research that showed the utility of this imaging to prevent unnecessary salvage surgery [Mehanna, et al]. PET response will be based on the "Hopkin's criteria."[Marcus et al.]. This is a five point scale with blood pool and liver as reference standard and accommodates FDG uptake due to post radiation inflammation and is outlined below.

Five-Point Qualitative Post-Therapy Assessment Scoring System (Hopkins Criteria) for Head and Neck PET/CT [38]

Score	^{18}F-FDG uptake pattern	Response Category
1	^{18}F-FDG uptake at the primary site and nodes less than IJV	Complete metabolic response
2	Focal ^{18}F-FDG uptake at the primary site and nodes great than IJV but less than liver	Likely complete metabolic response
3	Diffuse ^{18}F-FDGuptake at the primary site or nodes is greater than IJV or Liver	Likely post-radiation inflammation
4	Focal ^{18}F-FDGuptake at the primary site or nodes greater than liver	Likely residual tumor
5	Focal and intense ^{18}F-FDG uptake at the primary site or nodes	Residual tumor

Scores 1, 2, and 3, which represent complete metabolic response, likely complete metabolic response, and likely post-radiation inflammation, respectively, were considered negative for tumor and have a **Negative Predictive Value (NPV)**.

Scores 4 and 5, which represent likely residual tumor and residual tumor, respectively, were considered positive for tumor and have a **Positive Predictive Value (PPV)**. New lesion would be considered as progressive disease.
Salvage surgery decisions will be left the treatment team and should not be dictated by the PET imaging findings.

11.6 **Events of Clinical Interest Guidance Document**

See separate ECI Guidance Document

11.7 **Preclinical data (unpublished)**

PD-1 BLOCKADE SYNERGIZES WITH CISPLATIN RADIATION THERAPY AIDING IN CLEARANCE OF HPV+ OROPHARYNGEAL CARCINOMA

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Squamous cell carcinomas of the head and neck (SCCHN) are the 6th most common malignancy world-wide with approximately 650,000 diagnoses per year. Human papillomavirus (HPV) causes up to 80% of oropharyngeal (tonsil/base of tongue) SCCHN. Despite presenting at an advanced stage, multiple studies show that HPV+ SCCHN are more curable relative to their HPV- counterparts. Clearance of SCCHN during treatment with cisplatin radiation therapy (CRT) is not only related to direct cytotoxicity, but is also dependent on immune mediated clearance. This immune clearance is strongly dependent on an intact CD4+ and CD8+ cellular response to tumor cells harboring these viral oncogenes. Furthermore, the immune system recognizes and clears HPV + SCCHN only after the start of CRT. The immunologic tolerance to these cancers prior to treatment could be explained by immune checkpoints aimed at preventing unregulated immune activity. The programmed death 1 receptor (PD-1) and its ligand, PD-L1, are one such checkpoint axis. Recent data suggests that the PD-1:PD-L1 pathway may play an important role in immune resistance in head and neck cancer. We evaluated PD-1 in combination with CRT in an immune competent HPV+ SCCHN mouse model. HPV + mouse SCCHN cells were injected subcutaneously into immune competent mice and tumors were treated after growing to palpable size. Using the mouse analog to the human PD-1 blocker pembrolizumab, we determined that while single-agent therapy does not have significant activity on primary disease or distant metastasis, PD-1 blockade strongly synergizes with CRT. An overall survival of 58% was evident in mice treated with combination PD-1 and CRT versus 8% in mice treated with isotype control (IgG1) in combination with CRT ($p = 0.006$). These studies provide the impetus for future work investigating less toxic induction of immune responses in combination with blockade of immune checkpoint pathways.

11.8 Patient Reported Outcomes (PRO) – FACT H&N

FACT-H&N (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 <u>past 7 days</u>.**

	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

FACT-H&N (Version 4)

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

	EMOTIONAL WELL-BEING	**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 worse	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 now	0	1	2	3	4

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

	ADDITIONAL CONCERNS	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

_____

Patient Signature

_____

Date

11.9 List of Abbreviations

AE	Adverse Event
ADA	Anti-Drug Antibodies
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
APaT/ASaT	All Patients/Subjects as Treated Population
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
ß-HCG	Beta Human Chorionic Gonadotropin
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CrCl	Calculated Creatinine Clearance
CRF	Case Report Form
CRT	Chemo radiotherapy
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Antigen-4
CTV	Clinical Target Volume
DCA	Dichloroacetate
DKA	Diabetic Ketoacidosis
DLT	Dose Limiting Toxicity
DM	Distant Metastases
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
ERC	Ethics Review Committee
EU	European Union
FACT H&N	Functional Assessment of Cancer Therapy Head and Neck
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FFPE	Formalin-fixed Paraffin Embedded

FNA	Fine-Needle Aspirate
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GTV	Gross Tumor Volume
Gy	Gray
HCV	Hepatitis C
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee
IHC	Immunohistochemistry
IMRT	Intensity-modulated radiation therapy
irAEs	Immune-related Adverse Events
IRB	Institutional Review Board
irRECIST	Immune-related RECIST
ITIM	Immunoreceptor Tyrosine-based Inhibition Motif
ITSM	Immunoreceptor Tyrosine-based Switch Motif
IV	Intravenous
LA-SCCHN	Locally Advanced-Squamous Cell Carcinoma of the Head and Neck
LDH	Lactate dehydrogenase
LRC	Loco regional Control
mAb	Monoclonal Antibody
MDSCa	Myeloid-Derived Suppressor Cells
MEL	Melanoma
mg	Milligram
mg/kg	Milligram per Kilogram
mL	Milliliter
mm	Millimeters
MRI	Magnetic Resonance Imaging
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MTD	Maximum Tolerated Dose
NA or N/A	Not Applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NPV	Negative Predictive Value
NSAID	Non-Steroidal Anti-inflammatory Drug

OAR	Organs At Risk
ORR	Overall Response Rate
OS	Overall Survival
OTC	Over-the-counter
pCR	Pathologic Complete Response
PD	Progressive Disease
PET	Positron emission tomography
PFS	Progression Free Survival
PK	Pharmacokinetic
PK/PD	Pharmacokinetic-Pharmacodynamic
PO	Oral Administration
PPV	Positive Predictive Value
PR	Partial Response
PRO	Patient Reported Outcomes
PS	Performance Status
PTV	Planning Target Volume
QOL	Quality of Life
rCR	Radiographic Complete Response
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RTOG	Radiation Therapy Oncology Group
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	Standard of Care
SOP	Standard Operating Procedures
T1DM	Type 1 Diabetes Mellitus
TB	Bacillus Tuberculosis
TIL	Tumor-Infiltrating Lymphocytes
TNM	Tumor, node, and metastasis
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
WBC	White Blood Cell

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13.0 SIGNATURES

INVESTIGATOR'S STATEMENT

I agree to conduct the study as outlined in the protocol entitled "Phase IB study of Pembrolizumab in combination with chemo radiotherapy (CRT) for locally advanced squamous cell carcinoma of the head and neck (SCCHN)" in accordance with the guidelines set forth and all applicable government regulations.

READ AND ACKNOWLEDGED:

PRINCIPAL INVESTIGATOR	Date