COORDINATING CENTER: UPMC Hillman Cancer Center

TITLE: A Phase II trial of reirradiation combined with open label Pembrolizumab in patients with locoregional inoperable recurrence or second primary squamous cell carcinoma of the head and neck (SCCHN)

STUDY NUMBER: HCC #18-009

IND NUMBER: EXEMPT

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1.0 TRIAL SUMMARY

Abbreviated Title	Reirradiation combined with pembrolizumab (trade name: Keytruda®) in recurrent SCCHN
Trial Phase	Phase II
Clinical Indication	Locoregional recurrence or second primary SCCHN which is unresectable or the patient is unwilling to undergo resection who are able to undergo reirradiation
Trial Type	Interventional
Type of Control	NA-historical
Route of Administration	Intravenous
Trial Blinding	Unblinded
Treatment Groups	Single arm trial
Number of Trial Subjects	48 evaluable subjects
Estimated Duration of Trial	The estimated time from opening the trial to data analysis is approximately 36 months. This allows for accrual over 24 months and a minimum 12 month maturation period for all patients enrolled.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified evaluation. Each patient will undergo screening and then be treated with reirradiation with 1.2 Gy BID, 5 days a week (weeks 1-5). Pembrolizumab will be given at 200mg intravenous every 3 weeks starting day one or day two of reirradiation and will be continued in all patients until 3 months post completion of reirradiation, at which time a PET/CT will be done to evaluate response. Patients with progressive disease (PD) will be taken off the study. Patients that have a complete response (CR) will be followed clinically and radiographically, and if disease recurs may be eligible to be retreated with pembrolizumab for up to one year. Patients with partial response (PR) or stable disease (SD) will continue treatment with pembrolizumab for up to two years unless one of the following occurs: --documented confirmed disease progression --unacceptable adverse event(s) --intercurrent illness that prevents further administration of treatment --investigator decision to withdraw the subject --subject withdraw of consent --subject pregnancy --subject noncompliance --administrative reasons (i.e. trial is closed prematurely). Patients who have not progressed at completion of 24 months of therapy will be observed, but may be eligible for 1 year of retreatment with pembrolizumab if they develop recurrence/progression if they qualify as detailed in the protocol and if the trial is still ongoing.

2.0 TRIAL DESIGN

2.1 Trial Design

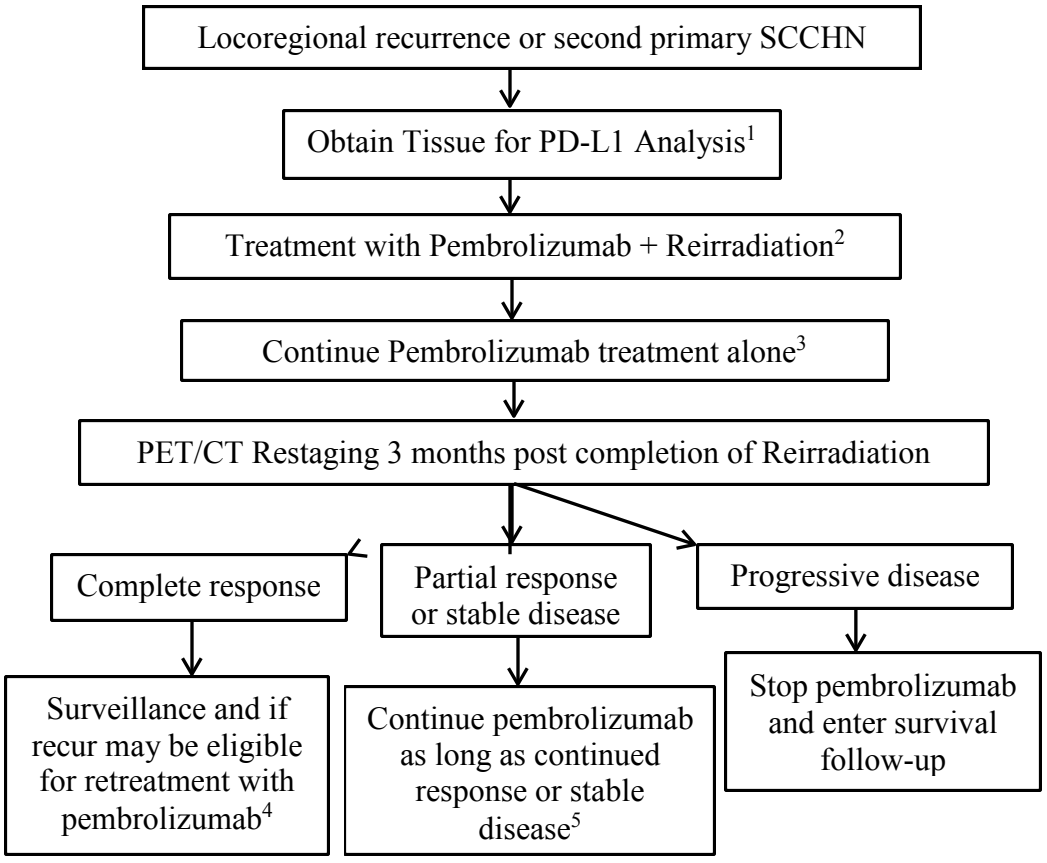
This is a single arm phase II clinical trial investigating the combination of open label anti- PD-1 mAb pembrolizumab (trade name: Keytruda®) and reirradiation (RT) in patients with locoregional inoperable recurrence or second primary SCCHN. The accrual goal is 48 patients. The primary endpoint is progression free survival (PFS). Secondary endpoints are toxicity, best overall response rate (RR), clinical benefit rate (CBR), time to in field progression, overall survival (OS), and patient reported quality of life as measured by the EORTC QLQ-C30 and EORTC QLQ-H&N35 questionnaires.

Patients that meet the eligibility criteria will undergo PET/CT for baseline imaging and will require tumor tissue for evaluation for PD-L1 expression. Fresh tissue or archival tissue will be obtained and used for PD-L1 analysis. PD-L1 expression will not be required for entry onto the study, given it is unknown if PD-L1 is predictive when pembrolizumab is combined with radiation, and given preclinical data suggesting that radiation leads to an increase in IFN-γ and subsequent PD-L1 expression in the tumor.[1] As highlighted in the study schema, patients will be treated with radiation (1.2Gy BID for total 60Gy) concurrent with pembrolizumab at 200mg intravenous every 3 weeks. The first dosage of pembrolizumab will be given on the first or second day of radiation. After completion of radiation treatment, patients will continue to receive pembrolizumab as a single agent for 3 months. At 3 months after completion of radiation, all patients will undergo a PET/CT to evaluate for response. Patients with a complete response (CR) at 3 months will discontinue pembrolizumab therapy and be observed with clinical exam and repeat CT neck at least every 3 months in the first year and every 6 months in year 2. These patients will then have continued annual follow-up with physical exam and CT neck (as clinically indicated) until the end of the study. Patients with a partial response or stable disease will continue treatment with pembrolizumab up to a total of 24 months (104 weeks) from the first cycle of treatment as long as they do not develop progressive disease, an intolerable toxicity, or other criteria for study withdrawal. These patients will be monitored with CT neck/chest after every 3rd cycle of pembrolizumab or more frequently if clinically indicated. Patients with progressive disease at 3 months post reirradiation will be taken off pembrolizumab and followed for survival. A patient who achieves a CR at 3 months post reirradiation and subsequently progresses may be eligible for retreatment with pembrolizumab as a single agent for up to one year. However, only the time to initial progression will be included in the PFS analysis, the primary endpoint of the study. Determination of response will be as per RECIST 1.l. However, given the experience with immune co-signaling blockade and the possibility of an inflammatory reaction leading to an increase in size of target lesions as well as the development of new lesions initially (before subsequent regression), progressive disease in the absence of clinical deterioration will be verified with repeat CT imaging not less than 4 weeks from prior imaging. [2,3]

While this will be the first time in humans that an anti-PD-1 mAb is combined with radiation, safety data with pembrolizumab as a single agent reveals no difference in toxicity at different dosages. It is, however, necessary to establish the safety of combining pembrolizumab with

radiation. Therefore, instead of a phase I component with dose escalation or de-escalation, this trial will be done as a phase II trial with a stop rule if the pre-specified acute non- hematologic toxicity boundary is crossed as detailed in the statistical consideration section 8.0. The first 20 patients enrolled on the study will be included in the pre-specified acute non-hematologic toxicity threshold evaluation. Toxicity will be evaluated using CTCAE v4.0, and pembrolizumab will be held for grade $\geq$ 4 acute radiation toxicity, or for all other grade $\geq$ 3 toxicities. If the first 20 patients complete reirradiation in combination with pembrolizumab (plus 2 weeks) without crossing the toxicity boundary, all subsequent patients to the goal of 48 total evaluable patients will be enrolled without a formal stop rule for toxicity. All patients will be evaluated for efficacy endpoints.

2.2 Trial Diagram



1. Tumor tissue for PD-L1 analysis from archival or fresh biopsy.
2. Cycles 1 and 2 of pembrolizumab given concurrent with reirradiation 1.2Gy BID Monday through Friday X 25 treatment days (weeks 1-5).
3. Continue treatment with pembrolizumab alone (cycles 3-6) (weeks 6-16).
4. Patients will be followed with imaging and clinical exams as per section 6.0, and if cancer recurs, they may be eligible for retreatment with pembrolizumab for 12 months.
5. Patients can continue treatment with pembrolizumab for up to 24 months (from initiation of treatment) as long as continue to respond or have stable disease.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

1) Objective: The primary objective is to evaluate the progression free survival (PFS) in patients with locoregional inoperable recurrence or second primary squamous cell carcinoma of the head and neck (SCCHN) treated with reirradiation in combination with pembrolizumab.

Hypothesis: The combination of pembrolizumab and reirradiation will lead to improved progression free survival in patients with locoregional inoperable recurrence or second primary SCCHN compared to historical outcomes with concurrent chemotherapy and reirradiation.

3.2 Secondary Objective(s) & Hypothesis(es)

1. **Objective**: To evaluate the safety and toxicity profile of the combination of reirradiation and pembrolizumab in patients with locoregional inoperable recurrence or second primary SCCHN.

   Hypothesis: The combination of pembrolizumab and reirradiation will be safe and show acceptable toxicity in the range of what is currently seen with concurrent chemotherapy with reirradiation. We hypothesize that pembrolizumab will not sensitize the tissue to reirradiation, as would be expected with traditional cytotoxic chemotherapy, but rather reirradiation will stimulate the immune system making pembrolizumab more efficacious. Therefore, we hypothesize that acute radiation toxicity should not be increased compared to that observed with concurrent chemotherapy and reirradiation.

2. **Objective**: To evaluate the best overall response rate (ORR) by RECIST 1.1 in patients with locoregional inoperable recurrence or second primary SCCHN treated with reirradiation combined with pembrolizumab.

3. **Objective**: To evaluate the clinical benefit rate (CBR) by RECIST 1.1 in patients with locoregional inoperable recurrence or second primary SCCHN treated with reirradiation combined with pembrolizumab.

4. **Objective**: To evaluate the time to in field progression in patients with locoregional inoperable recurrence or second primary SCCHN treated with reirradiation combined with pembrolizumab.

5. **Objective**: To evaluate the Overall Survival (OS) in patients with locoregional inoperable recurrence or second primary SCCHN treated with reirradiation combined with pembrolizumab.
6. **Objective**: To evaluate patient reported quality of life as measured by questionnaires EORTC QLQ-C30 and EORTC QLQ-H&N35 in patients with locoregional inoperable recurrence or second primary SCCHN treated with reirradiation combined with pembrolizumab.

3.3 Exploratory Objectives

The following exploratory post-hoc analyses will be carried out to evaluate:

1. Whether there is any correlation between PD-L1 expression on initial biopsy and the efficacy of pembrolizumab combined with reirradiation.

2. Whether there is any correlation between p16 expression in tumor biopsies and the efficacy of pembrolizumab combined with reirradiation.

3. Whether there is any correlation between percentages of Cytotoxic T cells (CTL), Regulatory T cells (Treg), or Myeloid Derived Suppressor cells (MDSC) in the peripheral blood at initiation of therapy, and efficacy of pembrolizumab combined with reirradiation.

4. Whether there is any correlation between changes in percentages of Cytotoxic T cells, Regulatory T cells, or Myeloid Derived Suppressor cells over time, and efficacy pembrolizumab combined with reirradiation.

5. Whether there is any correlation between irradiated volume of vascular structures (as evaluated by dose-volume histogram) and efficacy of pembrolizumab combined with reirradiation.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades[4]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies[5-9]. 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) [10,11]. The structure of murine PD-1 has been resolved[12]. 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[10, 13-15]. 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[16, 17]. 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[18, 19]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells[20]. 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[16, 21-23]. 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[16]. 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)[24]. 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 (previously known as SCH 900475) 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.

4.1.2 Preclinical and Clinical Trial Data with Pembrolizumab (summarized from Investigator's Brochure)

Preclinical data with pembrolizumab in melanoma, squamous cell carcinoma, pancreatic cancer, and colorectal cancer has shown that blockade of PD-1 interaction with PD-L1 and PD-L2 leads to activation and infiltration by cytotoxic CD8 T cells and subsequent regression of tumor. This has led to ongoing and completed clinical trials with pembrolizumab in melanoma, NSCLC, and numerous other advanced solid tumors including triple negative breast, urothelial cell cancer, head and neck cancer, and gastric cancer.

In PN001, the first in human study of pembrolizumab at three different dose levels in solid tumors, no DLT (dose limiting toxicity) or serious infusion reactions have been observed. Further details of the experience with pembrolizumab at different dose levels and rationale for ongoing dosing schedule are provided in section 4.2.2.1. In ongoing trials pembrolizumab has been generally well tolerated. The most common adverse events are fatigue, nausea, cough, pruritus, diarrhea and rash. The most commonly reported immune- related adverse events across the dose-schedules are rash, pruritus, vitiligo, hypothyroidism, arthralgia, diarrhea, and

pneumonitis. Further information about toxicity, including in SCCHN can be found in the pembrolizumab Investigator Brochure and Keytruda® package insert.

In melanoma, overall response rates with pembrolizumab monotherapy in ipilimumab exposed and ipilimumab naïve advanced melanoma were 25% and 39% respectively by central independent review by RECIST 1.1. Importantly responses were durable with a 1 year survival of 71% for all melanoma patients. Pembrolizumab was approved for use in advanced melanoma by the FDA in September 2014. Pembrolizumab has also gained FDA approval based on efficacy in advanced urothelial carcinoma, NSCLC, Hodgkin lymphoma, and SCCHN. Data for SCCHN is reported in section 4.2.1 below

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Squamous cell carcinoma of the head and neck (SCCHN) is the 6th most common malignancy worldwide.[25] For patients with locally advanced SCCHN, radiation is part of either initial definitive therapy or adjuvant therapy after surgical resection. Despite aggressive initial definitive therapy, patients with SCCHN are at high risk for the development of second primary tumors and a significant proportion of patients will recur, commonly within the first 2 years.[26, 27] The majority of these recurrences are locoregional and are associated with significant pain, disfigurement, and functional decline.[28] Unfortunately, a significant proportion of these patients will not have a salvage surgical option. Even with salvage surgery, local failure rates are upwards of 59%.[29]

Patients with locoregional recurrence or second primary without a surgical option are currently treated with reirradiation with concurrent chemotherapy. Reported outcomes from the largest trials that evaluated reirradiation with concurrent chemotherapy include a median PFS of 7-8 months and median OS of 10-12 months,[30-33] with even worse survival in patients who recurred within a year compared to patients recurring more than one year after primary radiation (median OS 5.8 vs. 9.8 months respectively, p = .036). [3] Improved outcomes are desperately needed for this patient population.

While concurrent chemotherapy is given with reirradiation, there is no data evaluating whether concurrent therapy improves outcome compared to reirradiation alone. Additionally, various chemotherapy regimens including Cisplatin/Paclitaxel, 5FU/hydrea, Docetaxel, Cisplatin/Docetaxel have been used concurrently without direct comparison of effectiveness and there is not one chemotherapy regimen that can be regarded as standard of care. [30-35]

Traditional chemotherapy sensitizes the tissue to radiation allowing for increased efficacy when given concurrent with radiation. However, this sensitization comes at the cost of increased hematologic and non-hematologic toxicity. In trials with reirradiation concurrent with chemotherapy for recurrent SCCHN, grade 4 and 5 acute toxicity rates are 16-23% and upwards of 5% respectively in the largest trials.[30-32, 34]

The PD-L1:PD-1 Pathway in SCCHN

Robust data supporting the significant role of the PD-L1:PD-1 pathway in SCCHN has led to ongoing clinical trials with single agent anti-PD-L1 and anti-PD-1 mAbs including pembrolizumab. In SCCHN, PD-L1 expression has been observed in 43-100% of patients,

across multiple primary sites.[35-36] (Table 1) Given the recognized importance of HPV in the etiology of oropharyngeal SCCHN, several investigators have now sought to correlate expression of PD-L1 with HPV status. Three independent studies have revealed higher expression of PD-L1 in HPV positive compared to negative patients: 70% vs. 29%,[37] 49.2% vs. 34.1%,[38] and 62.5% vs. 40%. [39] Importantly, PD-L1 expression has been observed in 43% and 70% of recurrent and metastatic patients, respectively.[37] PD-1 has been shown to be expressed on effector T cells in the tumor microenvironment in both HPV positive and negative SCCHN.[37,39]

Table 1. PD-L1 Expression in SCCHN [40]

Study	Primary Site	Sample Size	Percent of tumors with PD-L1 expression	Percent of tumors with PD-L1 expression in HPV positive cases	Percent of tumors with PD-L1 expression in HPV negative cases
Strome et al.	OC, HP, L, PNS	24	66	NA	NA
Ukpo et al.	OP	181	46.4	49.2	34.1
Lyford-pike et al.	OP	27	59	70	29
Badoual et al.	OC, OP, HP	64	51.5	62.5	40
Cho et al.	OC	45	87	NA	NA
Zhang et al.	NP	59	67.8	NA	NA
Hsu et al.	NP	25	100	NA	NA

OC-Oral Cavity; OP-Oropharynx; NP-Nasopharynx; HP-Hypopharynx; PNS-Paranasal Sinus; L- Larynx. NA–Non-Applicable

Multiple preclinical studies have shown the efficacy of blockade of the PD-1:PD-L1 pathway in a SCCHN model.[35, 36] Strome et al, transfected plasmid-encoding mouse PD-L1 into mouse SCC cell line SCCVII, creating a mouse model of SCCHN with tumor expression of PD-L1. Next they examined the efficacy of 10B5, a hamster mAB against mouse PD-L1 after adoptive T-cell therapy. Activated T-cells were prepared from mice that were preimmunized with SCCVII-pulsed dendritic cells and expanded in vitro by anti-CD3 and IL-2. All of the mice treated with these activated T cells and control IgG rapidly developed tumors and died within 40 days of inoculation with tumor. Therefore, T cell therapy alone was not effective. However the majority of mice treated with T cells and 10B5 remained alive more than 80 days. The survival of mice treated with T cells and anti-PD-L1 mAb was significantly improved compared to animals treated with T cells and control IgG.[35]

Preclinical data led to clinical trials with anti-PD-L1 mAb and anti-PD-1 mAbs including pembrolizumab. Reported clinical trial data with pembrolizumab in SCCHN led to the FDA granting accelerated approval for pembrolizumab in the treatment of recurrent or metastatic SCCHN with disease progression on or after platinum-containing chemotherapy. This was based on efficacy data in 174 patients with R/M SCCHN with an ORR of 16%. The median

duration of response has not been reached and the range of duration of response was 2.4 months to 27.7 months. Among the responding patients 82% had responses for 6 months or longer. [41]

The Immunogenic Effects of Radiation.
Inherent to the efficacy of PD-1 mAb blockade is the need for the immune system to be activated. The literature consistently shows that radiation can initiate and promote both innate and adaptive immunity against tumors by mechanisms including: 1. Enhanced expression of damage associated molecular patterns (DAMP), leading to stimulation of dendritic cells and subsequent increase in antigen presentation. 2. Enhanced expression of MHC class I molecules, adhesion molecules and stress-induced ligands, and death receptors on tumor cells leading to increased recognition and killing by T cells. 3. Induction of chemokines CXCL9, CXCL10 and CXCL16 promoting recruitment of effector CD 8 T cells.
4. Release of pro-inflammatory cytokines such as interleukin 1β, TNFα, IFNγ driving anti-tumor immunity.[42-44]

Radiation in combination with anti-PD-1 mAb and anti-PD-L1 mAb has shown synergy, with resultant increased efficacy compared to mAb or RT alone in glioblastoma multiforme (GBM) as well as colon and mammary cancer mouse models.[1, 45] For example Deng et al demonstrated that radiation plus anti-PD-L1 mAb lead to an increase in antigen specific CD8 T cells and a decrease in MDSCs, leading to significantly increased anti-tumor effect compared to RT alone or anti-PD-L1 mAb alone in a mammary cancer mouse model. Importantly, radiation led specifically to increased PD-L1 expression in tumor cells, additionally enhancing the effect of anti-PD-L1 mAb.[1] Zeng et al did a similar experiment in a GBM mouse model and found that the combination of anti-PD-1 mAb plus radiation led to significantly increased cytotoxic CD8 T cells and decreased Tregs in the brains of the mice as well as prolonged survival compared to radiation or anti-PD-1 mAb alone.[45] Additionally, they injected tumor cells in mice that were cured of tumor by the anti-PD-1 mAb and radiation, and found that at 60 days there was no growth of tumor in these mice, suggesting that effective immunologic memory had developed. [59] While the best schedule of radiation (single dose or fractionated) to promote immunogenic cell death has not been defined, there is preclinical data to suggest that a fractionated schedule is more immunogenic.[46, 47]

Specifically in SCCHN, studies have been done investigating the immunologic effects of radiation. Moyer et el, using a SCCHN mouse model, found that there was increased efficacy to the combination of intratumoral DC injections combined with chemoradiation compared to chemoradiation alone which was dependent on the presence of CD4, CD8, and NK (natural killer) cells. Importantly, they observed a decrease in intratumoral Tregs after treatment with chemoradiation.[48] Other studies have observed a decrease in T regs after radiation.[49, 50] These observations are important as Tregs promote immune tolerance. Tabachnyk et al evaluated the tumor microenvironment in 58 patients with SCC of the oral cavity who were treated with neoadjuvant chemoradiation using standard fractionated RT to 50.4 Gy with concurrent Cisplatin/5Fluorouracil chemotherapy, followed by surgical resection. They compared various tumor infiltrating lymphocytes in pretreatment biopsy with post resection tissue samples. They found that in the peritumoral stroma the most pronounced reduction was in Tregs with an increase in favorable CD8/Treg ratio in post resection peritumoral stroma after chemoradiation. Decrease in T regs, increase in dendritic cells, and increase in CD8/Treg ratio post

chemoradiation were each associated with improved survival. [49] Also in SCCHN treatment with radiation was associated with increased CD8 tumor infiltrating lymphocyte proliferative activity. [51]

While the combination of radiation and anti-PD-1 mAb or anti-PD-L1 mAb has not been combined in humans, there is data with anti-CTLA4 mAb Ipilimumab in combination with radiation. A phase I/II dose escalation trial was done in metastatic castrate resistant prostate cancer patients with Ipilimumab as a single agent, as well as following a onetime dosage of 8 Gy of radiation to 1-3 bone lesions. Importantly, no DLT was observed with the combination of radiation and ipilimumab, and the full dosage of 10mg/kg was expanded.[52] This lead to a phase III trial comparing radiation plus ipilimumab to radiation plus placebo in metastatic castrate resistant prostate cancer. The radiation and ipilimumab group showed a significant increase in PFS and PSA (prostate specific antigen) response. Importantly, the incidence and severity of immune-related adverse events were similar to those reported as single agent ipilimumab in melanoma.[53] Similarly, in a retrospective study of patients with melanoma treated with ipilimumab that had also received palliative radiation during their course, the combination was not associated with increased toxicity compared to historical controls of single agent ipilimumab therapy.[54] Thus, Ipilimumab, which is associated with higher toxicity than reported with anti-PD-1 or anti-PD-L1 mAb blockade,[55] did not show increased toxicity when combined with radiation.

Rationale for the Combination of Pembrolizumab and Reirradiation in SCCHN.
In summary, preclinical data strongly supports that radiation will lead to the stimulation of innate and adaptive immunity with subsequent blockade of PD-1 by mAb, having a synergistic effect leading to increased immune mediated destruction of tumor cells. Preclinical data provides strong support for the therapeutic potential of anti-PD-1 mAb blockade in SCCHN. Experience with pembrolizumab as a single agent in recurrent/metastatic SCCHN has shown promising activity. We hypothesize that the combination of reirradiation and pembrolizumab will have a synergistic effect and lead to improvement in progression free survival compared to historical controls in SCCHN patients who have developed inoperable locoregional recurrence or second primary squamous cell carcinoma in the head and neck region.

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Rationale for Dose Selection/Regimen/Modification of Pembrolizumab

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated, and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date.

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

scientific rationale for testing a Q2W and Q3W dosing schedule.

In Protocol 001, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed, while one randomized cohort evaluation of 10 mg/kg Q3W versus 10 mg/kg Q2W is ongoing. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive pembrolizumab at 2 mg/kg versus 10 mg/kg Q3W. The ORR was 26% (21/81) in the 2 mg/kg group and 26% (25/79) in the 10 mg/kg group. The proportion of subjects with drug related AE, grade 3-5 drug-related AE, serious drug-related AE, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group. PK data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q3W dosing schedule. Because Q3W dosing is more convenient for subjects, Q3W dosing will be further studied.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. Pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight-based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings and a dosage of 200mg fixed dose intravenous every 3 weeks will be tested in all future trials.

4.2.2.2 Rationale for Dose Selection/Regimen/Modification of Radiation.

The prescribed radiotherapy dose will be a total dose of 60 Gy given as twice daily fractions of 1.2 Gy per fraction. This dose and schedule is a validated reirradiation regimen.[26, 30, 56] The rational and specifics of the radiation plan are detailed in section 5.2.1. Radiation techniques that can be used in this trial include 3DCT, IMRT (Intensity-modulated radiation therapy), or IMPT (Intensity-modulated proton therapy). IMRT or IMPT is preferred over 3DCT.

Proton Therapy (IMPT) as an option for Reirradiation.

Reirradiation of recurrent or second primary HNSCC is emphasized as an indication for proton therapy. While the ability to use proton therapy in the treatment of patients with HNSCC is

more recent than IMRT, the use of protons as a treatment modality dates back to 1946[57] IMRT utilizes radiation portals in which the intensity of photon (X-ray) radiation varies throughout the field. To achieve high dose conformality for tumor targets and avoid critical normal structures, lower dose to non-target structures has to be increased. Therefore, normal non-target tissues receive a "low dose bath" of radiation with IMRT.

While X-rays deliver dose to tumor they also expose "exit dose" to normal tissues distal to the tumor; protons, however are able to "stop" precisely within tumors and therefore have no exit dose. Protons lose all their energy in the last few millimeters of their penetration in tissue resulting in a sharply localized peak of dose known as the Bragg Peak. Hence the desired dose can be placed precisely at any given depth within the patient, according to the energy given to each proton. Because protons are absorbed in the Bragg peak within the tumor, this ''dose bath'' to normal non target tissue seen in IMRT, can be reduced with proton radiation therapy.[58]

As the intensity of conventional photon radiation can be modulated to produce IMRT, the intensity of the proton radiation can also be modulated to produce intensity-modulated proton therapy (IMPT). This is achieved by a pencil beam scanning technique in which a small circular beam is scanned across the defined treatment field with the energy and intensity varying so that the dose in each voxel can be optimized. IMRT achieves two-dimensional optimization with modulation of the fluence occurring in the plane orthogonal to the beam direction. IMPT, in contrast, allows modulation of the fluence and the position of the Bragg peak. IMPT is therefore a three-dimensional optimization technique. IMPT has been shown to have a better ability to spare normal tissues than IMRT for the treatment of head and neck cancers. Sparing of normal tissue is especially important in reirradiation, however it should be noted that the dose to the target volume is the same with photons or protons. In addition protons are a low LET (linear energy transfer) radiation similar to photons and have a comparable biologic effect in tissue relative to photons.[59] Therefore, the most important difference with protons is their finite range in tissue, with subsequent decrease in dose bath to normal non target tissue.[60, 61] Additionally, proton radiation is not experimental in head and neck cancer as it has been used outside of protocols as part of standard of care in the primary treatment of HNSCC and in the reirradiation setting.[62-64]

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

4.2.3.1.1 Primary

The primary endpoint will be progression free survival (PFS), defined as the time from the date of initiation of treatment to the date of progression or death (whichever occurs first). This is a clinically relevant and appropriate endpoint for a phase II trial and one in which there are established historical comparisons based on previous reirradiation with concurrent chemotherapy trials. This endpoint encompasses prolonged stable disease which is important, given the propensity for pembrolizumab to lead to durable stable disease.

4.2.3.1.2 Secondary

Secondary endpoints include toxicity, overall survival, best overall response rate, clinical benefit rate, and time to in field progression. These are important and commonly used secondary endpoints in phase II trials. As detailed in Section 2.0 and 8.0, toxicity will be evaluated closely as this is an important end point for this trial. A stop rule is in place if the acute toxicity boundary is crossed, as detailed in Section 8.0.

Patient reported outcomes, as measured by questionnaires EORTC QLQ-C30 and EORTC QLQ-H&N35, will be evaluated as patient experienced morbidity and quality of life are important measures in the treatment of SCCHN patients. The EORTC QLQ-C30 is one of the most widely used cancer specific health related quality of life tools. It contains 30 items. It measures 5 functional dimensions (physical, role, cognitive, social, emotional), 6 single items (appetite loss, constipation, dyspnea, financial impact, sleep disturbance, diarrhea), 3 symptom items (fatigue, pain, nausea/vomiting) and a global health and quality of life scale.[65]

The EORTC QLQ-H&N35 is one of the most widely used tools for measuring quality of life in patients with SCCHN.[66] It consists of 7 multi-item scales, measuring problems with swallowing, pain in the mouth, speech, senses, social eating and social contact, and 11 single-item scales assessing problems with mouth opening, teeth, sticky saliva, dry mouth, coughing, feeling ill, use of nutritional supplements, use of feeding tube, weight gain and weight loss, and use of analgesics.[67] The EORTC QLQ-C30 and EORTC QLQ-H&N35 are validated tools for assessing quality of life in SCCHN and have been used in both recurrent/metastatic trials as well as radiation trials.[68, 69] They will be used at different times during this trial (as detailed in Section 6.0) to evaluate QOL of patients undergoing treatment.

4.2.3.2 Biomarker/Exploratory Research

The following exploratory post-hoc analyses will be done.

4.2.3.2.1 Tumor PD-L1 expression

Tumor PD-L1 expression will be measured in biopsy specimens obtained before entry and analyzed retrospectively. While PD-L1 expression will not be required for entry onto the trial, an increased response rate observed with anti-PD-1 and anti-PD-L1 mAb treatment in patients with baseline PD-L1 expression in NSCLC and melanoma has been observed.[70-72] Therefore, we will retrospectively evaluate whether baseline PD-L1 expression correlates with efficacy endpoints.

4.2.3.2.2 Peripheral blood levels of cytotoxic T cells (CTL), regulatory T cells (Treg), and myeloid derived suppressor cells (MDSC)

It will be important to study the effects of radiation in combination with pembrolizumab on the levels of cells of the immune system, including cytotoxic T cells, Tregs and MDSC, which have an important role in the immune response to malignancy. We will analyze percentages of CTLs, Tregs, and MDSCs in the peripheral blood over time. Serum will be drawn at initiation of therapy, completion of reirradiation, 3 months post completion of reirradiation, and at time of progression as detailed in Section 6.0. Percentages of these cells will be analyzed retrospectively by flow cytometry to see if there is any correlation with efficacy endpoints.

4.2.3.2.3 Human papilloma virus

HPV associated oropharyngeal cancer, as measured by p16 expression in tumor biopsy

specimens from oropharyngeal cancer patients by immunohistochemistry, has been associated with improved outcomes, including in the recurrent/metastatic setting. [73-76] Additionally, HPV associated tumors have been observed to have higher PD-L1 expression and increased density of tumor infiltrating lymphocytes as detailed in the background section. Therefore, we will evaluate p16 status in pretreatment tumor biopsies from oropharyngeal cancer patients to evaluate retrospectively, if p16 expression correlates with efficacy endpoints.

4.2.3.2.4 Irradiated volume of vascular structures

Different lymphocytes have varying degrees of sensitivity to radiation. Changes in radiation target volume size may alter the radiation dosage to circulating lymphocytes in the blood. Therefore, we will retrospectively analyze whether there was any correlation between irradiated volume of vascular structures during reirradiation and the efficacy of pembrolizumab combined with reirradiation.

4.2.3.3 Future biomedical research

With patient consent, the UPMC Hillman Cancer Center will conduct future biomedical research on blood and tumor tissue specimens collected during this clinical trial. This research may include but is not limited to genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes. Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial). The objective of collecting specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Patients with biopsy proven locoregional recurrence or second primary SCCHN in a previously radiated field which is unresectable or the patient is unwilling to undergo resection. Determination of unresectability will be based on multidisciplinary review of each case.

5.1.2 Subject Inclusion Criteria

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

1. Patients with biopsy proven locoregional recurrence or second primary SCCHN which is unresectable or the patient is unwilling to undergo resection.

2. Have received only one prior radiation treatment course. Prior radiation course must have been with curative intent.

3. At least a 6-month interval since completion of prior radiation.

4. Based on prior radiation records, have had most of the tumor volume (>50%) previously radiated at doses $\geq$ 45 Gy without exceeding spinal cord tolerance (combining previous and future radiation dose to 1cc of the spinal cord of $\leq$ 60 Gy).

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

6. Be willing to return to the center for all study-related follow up procedures, including blood collections and completion of imaging studies as required by the protocol.

7. Be willing to undergo percutaneous endoscopic gastrostomy (PEG) placement, if necessary.

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

9. Have at least one measurable area of disease based on RECIST 1.1 within the previously radiated field.

10. Provide adequate tissue (core or incisional/excisional biopsy) prior to starting study treatment. This tissue will be used for PD-L1 analysis. Fresh tissue or archival tissue sample can be used. If adequate tissue cannot be safely obtained than the patient may still be enrolled on the trial after discussion with the study principal investigator as long as FNA was done to confirm recurrent/second primary HNSCC.

11. Have a performance status of 0-1 on the ECOG Performance Scale.

12. Life expectancy of at least 12 weeks based on investigator estimate.

13. Demonstrate adequate organ function as determined by the labs in Table 2, performed within 21 days of treatment initiation.

Table 2. 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
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
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

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

15. 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 5.8.2). Women of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

16. 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.

17. Because informed consent and study materials will be in English, proficiency in English language is required.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject has any of the following:

1. Presence of distant metastatic disease.

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

3. 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.

4. Has had a prior monoclonal antibody, chemotherapy, or targeted small molecule therapy 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 (alopecia is an exception).

    a. Note: Subjects with ≤ Grade 2 neuropathy or ototoxicity are an exception to this criterion and may qualify for the study.
    b. Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

5. History of other malignancy within 5 years with the exception of prior SCCHN, adequately treated basal cell or squamous cell skin cancer, or carcinoma of the cervix.

6. Has an active autoimmune disease requiring systemic treatment within the past 3

months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic therapy or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study.

7. Has a history of non-infectious pneumonitis that required steroids, evidence of interstitial lung disease, or currently active non-infectious pneumonitis.
8. Has an active infection requiring systemic therapy.
9. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the 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.
10. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
11. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
12. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
13. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
14. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g. Hep C Ab positive with positive hepatitis C virus RNA PCR)
15. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

5.2 Trial Treatments

5.2.1 Radiation Treatment

5.2.1.1 Dose Fractionation

The prescribed radiotherapy dose will be a total dose of 60 Gy given as twice daily fractions of 1.2 Gy per fraction (total of 50 fractions and 25 intended treatments days), delivered at a minimum of 6 hours apart, five days a week for 5 consecutive weeks. This dose and schedule is a validated reirradiation regimen.[26, 30, 56] This reirradiation regimen is considered a standard of care regimen for treatment of locoregional recurrence or second primary SCCHN.

Radiation treatment can begin Monday through Wednesday. Dose-limiting normal tissue constraints are listed in Section 5.2.1.5, including a limit of 60 Gy total (prior plus current) to 1cc of the spinal cord. Missed treatments (for any reason) should be made up to reach the prescribed total radiation dose as detailed in Section 5.2.1.7.

5.2.1.2 Technical Factors

Patients will be treated with either photons alone or a combination of photons and electrons or with protons alone. Charged particle therapy will not be used. Those patients treated with photons will be treated using either the IMRT (intensity-modulated radiation therapy) preferentially or 3-D conformal techniques. Patients treated with protons will be treated with IMPT. Those patients whose recurrent tumor is in close vicinity of dental fillings would best be treated using IMRT rather than protons because of the stopping power of protons by the dental amalgam fillings. Otherwise, the choice of radiation modality will be determined by the treating radiation oncologist. Linear accelerators with appropriate photon and electron energies of 4 - 18 MV and/or 6-25 MeV must be used. Verification and quality assurance of isocenter placement, field placement, and dose distribution will be performed as per established departmental standards.

Proton therapy being a low-LET (linear energy transfer) radiation is similar in biological behavior to photons. There will be no difference in the prescribed dose to the target which will receive the same conformal dose with protons as with photons. The active scanning pencil beam technique using either the SFO (single-field optimization) or MFO (multiple- field optimization) technique will be used to best cover the target and provide maximal sparing of critical adjacent tissues. Whether proton or photon radiation is used, the same localization, simulation, immobilization requirements, target volume, and treatment planning will be used as described below.

5.2.1.3 Localization, Simulation, and Immobilization Requirements

Patients will be treated in supine or other proper positions with their arms down to facilitate the positioning of the shoulders as low as possible, without compromising patient comfort. Dentures should be removed and metal crowns should be covered with a shielding agent (beeswax) to prevent mucosal irritation. Pre-therapy extraction of extensively diseased teeth and gingiva should be carried out with conservation of restorable teeth where possible. At least 10 days should be allowed prior to the start of radiation for healing of gingivae post- extraction. Patients must be reproducibly immobilized in a thermoplastic (Aquaplast) mask including neck and shoulder immobilization whenever possible. When mask immobilization techniques are not possible due to patient discomfort, alternative techniques are allowed, but require stringent daily localization and imaging as described in Section 5.2.1.6 below. Radio- opaque markers should be used whenever possible to delineate the extent of nodal disease, skin involvement, and any gross disease.

CT Simulation is mandatory. CT scan thickness should be at most 0.3 cm through the region that contains the primary target volumes. Intravenous contrast is recommended to better delineate tumor volume. Tumor volume must be identifiable on the CT images. CT/MRI or CT-PET fusion techniques may be used for better tumor delineation.

5.2.1.4 Target Volumes

Gross tumor volume (GTV) is defined as the visible tumor and grossly enlarged lymph nodes on CT, MRI, PET-CT, or physical exam. No elective lymph node radiation will be performed. Clinical target volume, CTV = GTV + an isotropic expansion of 1.0 cm. In specific situations where a smaller expansion is deemed clinically necessary, a smaller expansion is acceptable in order to respect anatomic boundaries, or normal tissue dose constraints. Expansion of the GTV to CTV in the areas of natural boundaries such as bone should be per the physician's judgment. The minimum boundary of any CTV should be 2-3 mm deep to the skin unless clinically involved. Planning target volume, PTV = CTV + 0.3 cm isotropic margin. Total margins less than 1.0 cm around the GTV will be deemed an acceptable deviation only in instances of spinal cord or carotid artery encroachment. Partial miss of the GTV or gross tumor cut through is an unacceptable deviation.

5.2.1.5 Treatment Planning

Records of prior radiotherapy treatments will be obtained. Records will be reviewed to determine and record the dose received. Representative cross-sectional images of patient anatomy and plan data will be reviewed to determine the regions treated and doses received. Whenever possible, dose-volume histograms will be reviewed. Doses to critical organs at risk, to at least include the spinal cord, brainstem, and optic apparatus when in or adjacent to a treatment field, will be recorded. Dose to overlapping regions of the spinal cord must be limited to 60 Gy total (prior plus current) to 1cc. If the spinal cord constraints cannot be met or previous treatment data are not available, patients will not be offered treatment on study.

Radiation dose should be prescribed to an isodose line that encompasses the PTV. The inhomogeneity within the target volume should not exceed ±10% of the target dose. The following are treatment planning goals are listed in priority order (violation of goals 2-5 will not constitute study ineligibility; only goal 1 will be required for all patients):

1. The spinal cord max dose to 1 cc will be $\leq$60 Gy total (prior plus current).
2. 100% of the prescription dose should minimally cover 100% of the GTV.
3. 95% of the prescription dose should minimally cover 95% of the PTV.
4. No points should receive >105% of the prescription dose outside of the PTV.
5. If possible, avoid the development of hotspots over the carotid arteries.

Documentation (typically in the form of treatment plan report pdf) of both prior and current radiation treatment records must be submitted to the coordinating center within 1 week of starting treatment for quality assurance.

Dose-Volume Analysis:
Please note that coverage of the target volumes according to the criteria listed above should not be sacrificed in order to meet the dose constraint of any organ at risk, with the exception of the spinal cord. The following are general guidelines for organ at risk (OAR) constraints:

Organ at Risk	Dose Constraint

Retina	Max dose ≤45Gy
Optic nerves	Max dose ≤55Gy
Optic chiasm	Max dose ≤55Gy
Lacrimal glands	Max dose ≤30Gy
Brainstem	Max dose ≤54Gy
Cochleas	Max dose ≤35Gy
Spinal cord	V48 < 0.3cc
Parotid glands (each)	Mean <26Gy

D50% <30Gy

At least 20 cc <20Gy (combined)

Mandible	Max dose ≤ 60Gy
Oral cavity	Mean dose < 50 Gy
Brachial plexus	Max dose ≤60Gy

The following additional contours will be added for data collection, but will not be used for plan optimization or evaluation:

- Right carotid: common and internal carotid superiorly to base of skull, inferiorly to 2cm below PTV
- Left carotid: common and internal carotid superiorly to base of skull, inferiorly to 2cm below PTV
- Right lymphatics: neck LN levels II - IV, inferiorly to 2cm below PTV
- Left lymphatics: neck LN levels II - IV, inferiorly to 2cm below PTV

Right vascular structures (when intravenous contrast used): to include the internal carotid to the skull base, external carotid and named branches within 1 cm to the level of the maxillary artery, and internal jugular to the base of skull. Inferior extent 2cm below PTV.

Left vascular structures (when intravenous contrast used): to include the internal carotid to the skull base, external carotid and named branches within 1 cm to the level of the maxillary artery, and internal jugular to the base of skull. Inferior extent 2cm below PTV.
Organ-at-risk, target coverage, and secondary dosimetric endpoint data [found in Corollary Dosimetric Data form] should be documented in the form of DVH, clinical goals, and completed corollary data form and included in the treatment plan report sent to the coordinating

center.

5.2.1.6 Treatment Delivery and Verification

When 3-D conformal technique is used, a combination of lateral opposing fields, single fields, anterior and lateral wedge pair fields, and oblique fields may be used for the site of recurrent tumor. When IMRT is used, static or dynamic techniques may be utilized as per institutional preference. Beam/Isocenter localization films (portal films) or electronic portal images (EPIs) should be obtained for all photon and electron fields before and at least once a week during the whole course of radiation therapy. Similarly, in the case of proton treatments, orthogonal fields will be taken prior to each treatment delivery to verify and confirm the treatment localization.

Daily imaging is necessary to keep the PTV margin at 3mm.

For photon patients, on the first day of treatment, kV images should be obtained and the patient's position corrected by bony alignment, then a cone-beam CT (CBCT) should be obtained if available to ensure appropriate alignment of the treated volumes with the soft tissue anatomy. CBCT should be repeated on days #2 and #3 in order to establish a correlation between kV and CBCT. This may require a member of the primary team to help with alignments. Thereafter, daily kV and weekly CBCT should be performed. Alternatively, daily CBCT localization may be employed for patients unable to tolerate thermoplastic (Aquaplast) mask immobilization.

For proton patients, daily kV images should be obtained and the patient's position corrected by bony alignment. Since CBCT is not routinely available for proton therapy, patients receiving proton therapy should receive at least weekly re-simulation CT scans if CBCT is not available to assess for changes in tumor and/or patient anatomy as detailed below. If CBCT is available to proton patients, then at least weekly CBCT should be performed; re- simulation CT scans would then only be necessary if re-planning may be considered due to significant changes on CBCT.

Re-simulation for proton or photon patients should occur if the PTV no longer covers the entire GTV as seen on CBCT, if the patient's immobilization devices no longer fit properly due to weight loss or soft tissue swelling, or if there is $\geq$ 2.0 cm change in SSD. Re- simulation may also be considered if there is profound tumor regression that would affect immobilization or plan accuracy. Re-planning should be performed at the discretion of the treating physician and guided by the ability to maintain adequate target volume coverage and acceptable normal organ dose. Because even slight changes in tumor and normal tissue anatomy much more significantly affect target volume and normal tissue dose delivery from proton therapy versus photon therapy, re-simulation should especially be considered for patients receiving proton therapy. It is strongly recommended to re-simulate proton patients on a weekly basis, especially if CBCT is not available, or even more frequently based on the physician's clinical assessment of the patient.

5.2.1.7 Missed treatments

Treatment breaks must be clearly indicated in the treatment record. Protocol management of treatment breaks resulting from acute toxicity are described in section 5.3.2. Missed treatments

for any reason should be made up to reach the prescribed total radiation dose. Whenever possible, a sixth treatment day (i.e. Saturday or Sunday) may be added per week to complete all fractions within the originally planned treatment duration. Should a single fraction be missed (i.e. only one fraction delivered in a given day), treatment should be resumed as soon as feasible with the next planned fraction without any attempt to offset the schedule to complete treatment with two fractions in the final day. At no point should there be an interval less than 6 hours between fractions.

5.2.1.8 Documentation Requirements

At the completion of treatment, the following should be kept in patient's file:

1. The administration times of the RT
2. Daily treatment record
3. All isodose distributions
4. Simulation and portal films
5. Radiotherapy summary
6. CT/MRI documentation
7. Treatment (beam-on) duration.

5.2.2 Treatment with Pembrolizumab

The dosing of pembrolizumab is outlined below in Table 3.

Table 3. Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200mg	Q3W	IV infusion	Day 1 of each cycle	Experimental
The pembrolizumab dosing interval may be increased due to toxicity as described in Section 5.4.2					

Treatment with pembrolizumab should begin on Day 1 or Day 2 of radiation. Doses of pembrolizumab during radiation treatment can be given before or after the first radiation treatment of the day.

5.3 Dose Selection/Modification of Radiation Therapy

5.3.1 Dose Selection

The rationale for selection of radiation dosing and schedule of treatment to be used in this trial is provided in Section 5.2.1.

5.3.2 Radiation Therapy Toxicity Evaluation and Dose Modification

All acute radiation toxicities (defined as toxicities occurring within 90 days from therapy start) will be graded according CTCAE v.4.0. During treatment with reirradiation plus concurrent chemotherapy, Grade 3, therapy-induced, acute non-hematologic toxicities have been observed in upwards of 30-50% patients.[56 30-32, 34] Common acute radiation adverse events in this patient

population include mucositis, pain, esophagitis, dysphagia, fatigue, weight loss, regional alopecia, xerostomia, hoarseness, transient ear discomfort, dysgeusia, and skin erythema and desquamation within the treatment fields. Nutritional evaluation prior to the initiation of therapy is highly recommended. Placement of a prophylactic gastrostomy tube or PEG tube during therapy will be at the discretion of the treating physician. In the case of severe weight loss, the use of tube feedings is encouraged as it is anticipated to minimize further treatment interruptions.

Late toxicities (defined as toxicities occurring after 90 days of therapy initiation) will be graded according to CTCAE v4.0. Late toxicities can include permanent xerostomia and occasionally persistent dysphagia. Less common long-term treatment adverse events include: hypothyroidism, loss of hearing, chronic swallowing dysfunction requiring permanent feeding tube, and cervical fibrosis. Rarer late radiation adverse events include: mandibular osteoradionecrosis and cervical myelopathy. Special attention should be directed in follow-up exams to any numbness or paresthesia, particularly in the first 6-12 months of follow-up. There is a relatively small, but real risk of carotid rupture in patients whose tumors overlap the carotid artery. Most of these events have occurred in association with active tumor in this region and may not necessarily be due to adverse effects of treatment.

Every effort should be made to continue radiation therapy without interruption. Grade 3 acute radiation toxicity is expected in a significant proportion of cases and should, in general, not lead to interruption of radiation therapy. However, interruptions in radiotherapy may be necessitated by $\geq$ grade 4 skin or mucosal toxicity or uncontrollable pain. Should severe radiation associated toxicity such as confluent mucositis, moist desquamation unresponsive to topical dressings, or severe stomatitis resulting in weight loss greater than 15% occur, treatment may be interrupted in order to relieve morbidity at the sole discretion of the treating radiation oncologist. If a treatment delay for acute toxicity is required, the total RT dose and dose per fraction will not be modified. Note, that any grade 4-5 acute radiation toxicity that occurs within 7 weeks of initiation of therapy counts toward the early stopping rule which is detailed in Section 8.0.

Acute local toxicity attributable to radiation effects ($\leq$ grade 3) and not pembrolizumab should be managed accordingly with optimal supportive care measures. If toxicity $\geq$ grade 4 persists, then a radiation break is allowable as defined above. Every effort should be made to avoid breaks in radiation treatment. If pembrolizumab is held due to other toxicity attributed solely to the pembrolizumab, as discussed in section 5.4.2, the radiation therapy should be continued.

Patients will be seen by a radiation oncologist each week during Weeks 1-7 for directed physical exam and toxicity evaluation. After the seventh week they will be seen at least once a month until 3 months after completion of radiation. This is detailed in table 6.1.

5.4 Dose Selection/Modification for Pembrolizumab

5.4.1 Dose Selection for Pembrolizumab

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

Pembrolizumab will be given at a dosage of 200mg intravenously every 3 weeks for all patients.

5.4.2 Pembrolizumab Toxicity Evaluation and Dose Modification

Toxicity from pembrolizumab will be graded by CTCAE v4.0. Pembrolizumab will be withheld for drug-related grade 4 hematologic toxicities. As discussed above, due to the expectation of significant grade ≤ 3 acute radiation toxicity with reirradiation, treatment with pembrolizumab will only be held for acute radiation toxicity that is grade 4, and resumed when this toxicity is $\leq$ grade 3. Acute radiation toxicity includes pain, local skin toxicity, mucositis/esophagitis, dysphagia, odynophagia, weight loss, hoarseness, regional alopecia, xerostomia, transient ear discomfort, or other toxicity that in the investigators opinion is from acute radiation toxicity. Pembrolizumab will be held for grade ≥ 3 non-hematologic toxicity attributed to pembrolizumab rather than radiation. If the patient requires a treatment break from radiation and the patient is due for the next dosage of pembrolizumab during the time of a treatment break, then that dosage of pembrolizumab will be held. The next dosage of pembrolizumab will be given on the first Monday after resumption of radiation treatment and continued every 3 weeks as per protocol.

Table 4. Pembrolizumab dose modification guidelines for drug-related adverse events

Toxicity	Grade	Hold Treatment (Y/N)	Timing for Restarting Treatment	Dose/Schedule for Restarting Treatment	Discontinue Subject (after consultation with Sponsor)
Hematological Toxicity	1, 2	No	N/A	N/A	N/A
	3*	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week**	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
	4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week**	
Non-hematological toxicity Note: Exception to be treated similar to grade 1 toxicity: • Grade 2 alopecia • Grade 2 fatigue For additional information regarding Adverse Events with a potential Immune-Etiology reference Section 5.7.2.	1	No	N/A	N/A	N/A
	2	Consider withholding for persistent symptoms	Toxicity resolves to Grade 0-1 or baseline	*Clinical AE resolves within 4 weeks*: Same dose and schedule (reference Section 5.7.3 for recommendations regarding pneumonitis) *Clinical AE does not resolve within 4 weeks:* May increase the dosing interval by 1 week for each occurrence**	Toxicity does not resolve within 12 weeks of last infusion
	3***, 4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week for each occurrence**	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*

*Excluding Grade 3 neutropenia, anemia, and thrombocytopenia ;
** The dosing interval can be increased to every 4 weeks. If toxicity resolves to grade 0-1 or baseline the dosing interval can be decreased to every 3 weeks again at the discretion of the investigator;
*** Pembrolizumab will be held for a grade 3 or 4 toxicity that is considered related to pembrolizumab. However a grade 3 toxicity that is considered an acute radiation toxicity will not require holding of pembrolizumab unless radiation therapy is on hold. Pembrolizumab will be held for a grade 4 acute radiation toxicity. Pembrolizumab can be restarted when acute radiation toxicity improves to grade $\leq$3.

In case a drug related toxicity that is not a toxicity associated with radiation does not resolve to grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued after consultation with the Sponsor. With investigator and Sponsor agreement, subjects with a laboratory adverse event still at grade 2 after 12 weeks may continue treatment in the trial

only if the adverse event is asymptomatic and controlled. For information on medications to manage adverse events, see Section 5.7.

Subjects who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of pembrolizumab should be discontinued from trial treatment.

5.4.3 Timing of Dose Administration

Trial treatment should be administered after all procedures/assessments have been completed as detailed in Section 6.0. The first dosage of pembrolizumab should be given on the first or second day of radiation. Every effort should be made to give the second pembrolizumab dose on a Monday as well. Doses of pembrolizumab during radiation treatment can be given before or after the first radiation treatment of the day. Subsequent pembrolizumab treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

Pembrolizumab will be administered as a 30 minute IV infusion (treatment cycle intervals may be increased due to toxicity as described in Section 5.4.2). Every effort should be made to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

5.5 Trial Registration

This is an open-label, single arm trial. All patients will undergo the study treatment. The investigator and subject will know the treatments and dosages administered.

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 schedule may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the Investigator and the subject.

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 supplement, and IV medications. 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 30 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 (events of clinical interest) 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 (including retreatment for post-complete response relapse) of this trial:

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, tuberculosis (bacille Calmette-Guerin—BCG), and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines and are not allowed.
- Glucocorticoids for any purpose other than the treatment or prophylaxis of any adverse event (intermittent use of bronchodilators or local steroid injections is allowed).

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

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

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.7 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, including, but not limited to the items outlined below. Additional details are provided in the event of clinical interest and immune-related adverse event guidance document Section 12.

- Diarrhea: 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). In symptomatic subjects, infectious etiologies should be ruled out. If symptoms are persistent and/or severe, endoscopic evaluation should be considered.
    - In subjects with severe enterocolitis (grade 3), pembrolizumab will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to grade 1 or less, corticosteroid taper should be started and

continued over at least 1 month.
    - In subjects with moderate enterocolitis (grade 2), pembrolizumab should be withheld and anti-diarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. For guidelines for continuing treatment with pembrolizumab, see Section 5.4.2.
    - All subjects who experience diarrhea 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.
- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.
- Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.
- Immune-related adverse events: Please see Section 5.7.2 below and the separate guidance document in appendix Section 12 regarding diagnosis and management of adverse experiences of a potential immunologic etiology.
- Management of infusion reactions: Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both types of AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: allergic reaction/hypersensitivity (including drug fever); arthralgia (joint pain); bronchospasm; cough; dizziness; dyspnea (shortness of breath); fatigue (asthenia, lethargy, malaise); headache; hypertension; hypotension; myalgia (muscle pain); nausea; pruritus/itching; rash/desquamation; rigors/chills; sweating (diaphoresis); tachycardia; tumor pain (onset or exacerbation of tumor pain due to treatment); urticaria (hives, welts, wheals); vomiting.

Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 5. Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs	**Stop infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: • IV fluids Antihistamines NSAIDS • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: • Diphenhydramine 50 mg po (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

5.7.2 Supportive Care Guidelines for Events of Clinical Interest and Immune-related Adverse Events (irAEs)

Events of clinical interest of a potential immunologic etiology (irECIs) may be defined as an adverse event of unknown etiology associated with drug exposure and is consistent with an immune phenomenon. irAEs may be predicted based on the nature of the pembrolizumab compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment. Additional details are provided in the Event of Clinical Interest and Immune-Related Adverse Event Guidance Document (Section 12).

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE. Information on how to identify and evaluate irAEs has been developed and is included in the Event of Clinical Interest and Immune-Related Adverse Event Guidance Document (Section 12). Subjects who develop a grade 2 or higher irAE should be discussed immediately with the Sponsor.

Recommendations to managing irAEs not detailed elsewhere in the protocol are detailed in Table 6.

Table 6. General Approach to Handling irAEs

irAE	**Withhold/Discontinue Pembrolizumab?**	**Supportive Care**
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold pembrolizumab	Consider systemic corticosteroids in addition to appropriate symptomatic treatment
Grade 3 and Grade 4	Withhold pembrolizumab Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 12 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.

5.7.3 Supportive Care Guidelines for Pneumonitis

Subjects with symptomatic pneumonitis should immediately stop receiving pembrolizumab and have an evaluation. The evaluation may include bronchoscopy and pulmonary function tests to rule out other causes such as infection. If the subject is determined to have study drug associated pneumonitis, the suggested treatment plan is detailed in Table 7.

Table 7. Recommended Approach to Handling Pneumonitis

Study Drug Associated Pneumonitis	Withhold/Discontinue Pembrolizumab?	Supportive Care
Grade 1 (asymptomatic)	No action	Intervention not indicated
Grade 2	Withhold pembrolizumab, may return to treatment if improves to Grade 1 or resolves within 12 weeks	Systemic corticosteroids are indicated. Taper if necessary.
Grade 3 and Grade 4	Discontinue pembrolizumab	Systemic corticosteroids are indicated. The use of infliximab may be indicated as appropriate. Refer to the Event of Clinical Interest and Immune-related Adverse Event Guidance Document (Section 12) for additional recommendations.

For grade 2 pneumonitis that improves to ≤ grade 1 within 12 weeks, the following rules should apply:

- First episode of pneumonitis
  - May increase dosing interval by one week (q 4 weeks) in subsequent cycles
- Second episode of pneumonitis – permanently discontinue pembrolizumab if upon rechallenge subject develops pneumonitis ≥ grade 2

5.8 Diet/Activity/Other Considerations

5.8.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AEs such as diarrhea, nausea or vomiting, mucositis, or dysphagia. Consultation with nutrition during radiation therapy is strongly recommended.

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 the screening visit throughout the study period up to 120 days after the last dose of study therapy.

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

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

5.8.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the sponsor and to Merck without delay and within 24 hours 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 information to the sponsor and to Merck. If a male subject impregnates his female partner, the study personnel at the site must be informed immediately, and the pregnancy must be reported to the sponsor 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.

5.9 Subject Withdrawal, Replacement and Criteria for Early Trial Termination

5.9.1 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the Investigator 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 treatment for any of the following reasons:

- The subject withdraws consent.
- Confirmed radiographic disease progression. See Section 7.1.2.6
- Unacceptable adverse events as described in Section 5.4.2
- 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

- Completed 24 months of treatment with pembrolizumab
    - Note: 24 months (104 weeks) of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to 12 months of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.2.1.
- Administrative reasons

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

5.10 Subject Replacement Strategy

A subject that withdraws from the trial for reasons other than toxicity, progression of disease or death and withdraws before the initial efficacy evaluation (PET/CT done at 3 months after completion of radiation) can be replaced. These cases will be recorded and accounted for in the report of the trial.

5.11 Criteria for Early Trial or Performance Site Termination

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

1 Quality or quantity of data recording is inaccurate or incomplete.
2 Poor adherence to protocol and regulatory requirements.
3 Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects.
4 If acute radiation toxicity threshold is crossed by the first 20 patients enrolled as detailed in Section 8.0, discussion with Merck will ensue and trial may be closed early.
5 Plans to modify or discontinue the development of the study drug.

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

6.0 TRIAL FLOW CHARTS

6.1 Initial Treatment Phase

Trial Period:	**Screening Day -28 to -1**	**Radiation + Pembrolizumab Treatment [1]**		**Pembrolizumab Monotherapy (Weeks 6-16)[2]**				**3 Months Post Radiation Imaging[3]**
Radiation Treatment (1.2Gy BID Monday–Friday x25 days)		**Treatment with radiation 1.2Gy BID Monday –Friday X 25 treatment days (weeks 1-5)**						
Pembrolizumab Treatment (Day 1 of each 21 Day Cycle):		**Cycle 1, Day 1**	**Cycle 2, Day 1**	**Day 1, Cycles 3-6**				**Week 17 +/- 7 days**
Scheduling Window (Days):		**+ 1 day**	**+1 day**	**+/- 3 days**				
Administrative Procedures								
Informed Consent	X							
Inclusion/Exclusion Criteria		X						
Demographics and Medical History	X							
Prior and Concomitant Medications	X	X	X	X	X	X	X	X
SCCHN History and Treatment	X							
Pembrolizumab Treatment Administration		X	X	X	X	X	X	X[9]
Clinical Procedures/Assessments								
Review Adverse Events[1]	X	X	X	X	X	X	X	X
Full Physical Examination	X			X				X
Directed Physical Examination[1]		X	X		X	X	X	
Vital Signs and Weight[5]	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X
Dental Evaluation [6]	X							
12 Lead EKG	X						X	
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory								
Pregnancy Test – Urine or Serum β-HCG[7]	X							
PT/INR and aPTT[12]	X							
CBC with Differential[8]	X	X	X[15]	X	X	X	X	

Trial Period:	**Screening Day -28 to -1**	**Radiation + Pembrolizumab Treatment [1]**		**Pembrolizumab Monotherapy (Weeks 6-16)[2]**				**3 Months Post Radiation Imaging[3]**
Radiation Treatment (1.2Gy BID Monday–Friday x25 days)		**Treatment with radiation 1.2Gy BID Monday –Friday X 25 treatment days (weeks 1-5)**						
Pembrolizumab Treatment (Day 1 of each 21 Day Cycle):		**Cycle 1, Day 1**	**Cycle 2, Day 1**	**Day 1, Cycles 3-6**				**Week 17**
Scheduling Window (Days):		**+ 1 day**	**+1 day**	**+/- 3 days**				**+/- 7 days**
Comprehensive Serum Chemistry Panel[14]	X	X	X[15]	X	X	X	X	
Urinalysis	X						X	
T3, FT4 and TSH	X						X	
Hepatitis C Ab[16]	X							
HBsAg, HBsAb	X							
HIV 1/2 Antibodies	X							
Efficacy Measurements								
PET/CT [3]	X							X[9]
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood								
Archival or Fresh Tissue Collection[10]	X							X[13]
Correlative Studies Blood Collection/Blood for Future Biomedical Research[4, 10]		X		X				X
Patient Reported Outcome Measures[11]								
EORTC QLQ C-30	X	X	X	X		X		X
EORTC QLQ-H&N35	X	X	X	X		X		X

1. During radiation treatment, patients will be evaluated weekly with a directed physical exam and toxicity evaluation (patients will be evaluated more frequently if clinically indicated). The first dose of pembrolizumab should be given on the first day of radiation (+ 1 day) Radiation treatment can begin Monday through Wednesday. Doses of pembrolizumab during radiation treatment can be given before or after the first radiation treatment of the day.
2. During the time period between completion of Radiation + Pembrolizumab Treatment and the 3 Months Post Radiation Imaging, the patient will be seen at Weeks 6 and 7, then at least once a month by a radiation oncologist. The patient will be seen before each pembrolizumab dose by a medical oncologist.

3. Baseline tumor evaluation and tumor efficacy assessment at 3 months after completion of reirradiation will be with PET/CT. CT will include diagnostic CT with contrast of neck/chest/abdomen/pelvis. If the investigator feels that MRI will be the best way to follow the patients head and neck disease subsequently, then an MRI of the neck should be done at baseline as well. However, CT scan is encouraged over MRI. For the initial PET/CT done during the screening procedures, the diagnostic CT scans need to be done within 28 days of the start of therapy while the PET can be done within 42 days of start of therapy.
4. Blood (approximately 2 teaspoons) will be drawn for correlative studies. Tumor and additional blood (approximately 2 teaspoons) for future biomedical research (FBR) is optional, but patient consent must be obtained be prior to sample collection. If a patient does not consent for FBR then only blood for correlative studies will be drawn. Blood draws for correlative studies and FBR will be into a Na Heparin "green top" tube (1 tube for each). They will be drawn prior to dosage of pembrolizumab at first and third cycle, and additionally at week 17 visit and at visit at time of progression.
5. Vital signs to include temperature, pulse, respiratory rate, blood pressure, and oxygen saturation as measured by pulse oximeter. Height will be recorded at screening visit only.
6. Prior to radiation therapy a dental evaluation will be done if recommended by treating radiation oncologist. Extraction of extensively diseased teeth should be carried out with conservation of restorable teeth where possible. At least 10 days should be allowed for healing of gingivae post-extraction. Because dental evaluation would be required for reirradiation as part of standard of care this evaluation/treatment can begin before consent for the trial.
7. For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to first dosage of pembrolizumab. If a urine pregnancy result can't be confirmed as negative, then a serum pregnancy test will be required. Pregnancy testing may be repeated if pregnancy is suspected.
8. CBC to include white blood cells, hgb/hct, platelets and differential. CBC as part of screening for organ function (Inclusion criteria # 13) is required to be done within 21 days of start date
9. Tumor imaging will determine the subsequent study treatment plan. Definition of response is detailed in section 7.1.2.6. Subjects with a complete response (CR), partial response (PR), and progressive disease (PD) will require confirmation by repeat CT scan. Subjects will remain on pembrolizumab following section 6.3 until response confirmation. Subjects with confirmed CR will follow Chart 6.2. Subjects with confirmed partial response **or who have** stable disease will **continue** to follow Chart 6.3. Subjects with confirmed progressive disease will follow Chart 6.4. See section
7.1.2.6 for all details on definitions of response.
10. Provide adequate tissue (core or incisional/excisional biopsy) prior to starting study treatment. This tissue will be used for PD-L1 analysis. Fresh tissue or archival tissue sample can only be used. If adequate tissue cannot be safely obtained than the patient may still be able to be enrolled on the trial after discussion with the study principal investigator, as long as FNA was done to confirm recurrent/second primary HNSCCIf the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR.
11. Patient Reported Outcome Measures will be completed by the patient. The EORTC QLQ C-30 should be completed first.
12. Coagulation studies will be repeated as clinically necessary.
13. A repeat biopsy may be needed to confirm disease status. See section 7.1.2.6.4 Assessment of Disease
14. Comprehensive serum chemistry panel is done as part of screening for organ function (inclusion criteria #13) is required within 21 days of start date
15. Starting with cycle 2 of pembrolizumab, CBC and CMP required prior to giving dosage can be done within 48 hours of dosage.
16. If Hep C Ab is positive a Hep C virus RNA PCR can be checked. If the Hep C virus RNA PCR is negative then the patient does not have active Hep C and therefore would still qualify for the trial.

6.2 Follow Up Phase for Patients Who Achieve a CR at Any Point During the Study or Who Complete Up to 24 Months of Pembrolizumab Without Progression of Disease. [1]

Trial Period: Follow Up	**Visits during the first year after the last dosage of pembrolizumab[2]**				**Visits during the second year after the last dosage of pembrolizumab [3]**		**Annually after 24 M visit**
	3M	**6M**	**9M**	**12M**	**18M**	**24M**	**Annually**
Visit Window	**+/- 2Wk**	**+/- 2Wk**	**+/- 2Wk**	**+/- 2Wk**	**+/- 2Wk**	**+/- 2Wk**	**+/- 2 weeks**
Clinical Procedures/Assessments							
Concomitant Medication Review	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X
Directed Physical Examination	X	X	X	X	X	X	X
Vital Signs and Weight[7]	X	X	X	X	X	X	X
Efficacy Measurement							
Tumor Imaging[4,5]	X	X	X	X	X	X	X[8]
Laboratory Procedures/Assessments							
Comprehensive Serum Chemistry Panel	X	X	X	X	X	X	X
CBC with Differential	X	X	X	X	X	X	X
T3, FT4 and TSH				X		X	X
Patient Reported Outcomes [6]							
EORTC QLQ C-30	X	X	X	X	X	X	X
EORTC QLQ-H&N35	X	x	X	X	X	X	X

1. Patients will undergo follow up as per this table until progression, withdrawal of consent, initiation of non-protocol anti-cancer treatment(s) or death, whichever occurs first. Definition of "first year" and "second year" are from the time of last pembrolizumab dosage. Patients who recur or progress may be eligible for retreatment discussed in section 7.1.5.2.1.
2. During the first year of follow up patients will be seen at least every 3 months. The patient can be seen more frequently if clinically indicated.

3. During the second year of follow up patients will be seen at least every 6 months. The patient can be seen more frequently if clinically indicated.
4. During the first year of follow up patients will undergo neck CT with IV contrast every 3 months to evaluate for recurrence. CT chest with IV contrast or CXR PA/Lateral will be done at the discretion of the investigator, as clinically indicated. This will be obtained prior to each 3 month visit. If the patient has evidence of recurrence on CT scan, a biopsy will be done. If recurrence is confirmed, the patient can be treated with pembrolizumab again as per the treatment flow chart 6.3. Patients can be retreated with pembrolizumab for up to one year. If the investigator feels that MRI will be the best way to follow the patients head and neck disease subsequently, then an MRI of the neck should be done at baseline as well. However, CT scan is encouraged over MRI.
5. During the second year of follow up patients will undergo neck CT with IV contrast every 6 months to evaluate for recurrence. CT chest with IV contrast or CXR PA/Lateral will be done at the discretion of the treating physician, as clinically indicated. This will be done prior to each 6 month visit. If the patient has evidence of recurrence on imaging, a biopsy will be done. If recurrence is proven, the patient may be eligible to be treated with pembrolizumab again as per table 6.3 below (Treatment phase for patients with PR/SD at 3 months post radiation). Patients can be retreated with pembrolizumab for up to one year. If the investigator feels that MRI will be the best way to follow the patient's head and neck disease subsequently, then an MRI of the neck should be done at baseline as well. However, CT scan is encouraged over MRI.
6. Patient Reported Outcome Measures will be completed by the patient. The EORTC QLQ C-30 should be completed first.
7. Vital signs to include temperature, pulse, respiratory rate, blood pressure, and oxygen saturation as measured by pulse oximeter.
8. Imaging will be done as clinically indicated.

6.3 Treatment Phase for Patients with a Partial Response (PR) or Stable Disease (SD) on Imaging 3 Months Post Completion of Radiation.[1]

Trial Phase	**Treatment Cycle**									**Treatment Cycle**
Treatment Cycle/Scheduled Time (Pembrolizumab Day 1 of each 3-week Cycle)	7	8	9	10	11	12	13	14	15	16 and beyond[2]
Scheduling Window (days): +/- 3 days										
Clinical Procedures/Assessments										
Review Adverse Events	X	X	X	X	X	X	X	X	X	X
Directed Physical Exam	X	X	X	X	X	X	X	X	X	X
Vital Signs and Weight[6]	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X
Laboratory Procedures/Assessments										
CBC with Differential	X	X	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel	X	X	X	X	X	X	X	X	X	X
Urinalysis[3]				X				X		X[3]
T3, FT4, TSH[3]				X				X		X[3]
Patient reported outcomes										
EORTC QLQ C-30	X		X		X		X		X	X[4]
EORTC QLQ-H&N35	X		X		X		X		X	X[4]
Efficacy Measurements										
Tumor Imaging[5]			X[5]			X[5]			X[5]	X[5]

1. Patients that develop a complete response during this phase of treatment will be followed as per table 6.2.
2. Patients will continue treatment with pembrolizumab for up to 24 months (from first dosage) or until progression of disease, complete response, discontinuation because of toxicity, or withdrawal from study.
3. Urinalysis and T3, FT4, TSH to be drawn before every 4th cycle (i.e. Cycle 18, Cycle 22, etc.).
4. EORTC QLQ C-30 and EORTC QLQ-H&N35 will be filled out by the patient every other cycle. The EORTC QLQ C-30 should be completed first.
5. Tumor imaging with CT neck and chest with IV contrast will be obtained after each 3rd cycle (or sooner if clinically indicated) Imaging should be reviewed to determine disease status prior to giving every 4th cycle . Definition of response is as per section 7.1.2.6.4. If the investigator feels that MRI will be the best way to follow the patient's head and neck disease subsequently, then an MRI of the neck should be done at baseline as well. However, CT scan is encouraged over MRI.
6. Vital signs to include temperature, pulse, respiratory rate, blood pressure, and oxygen saturation as measured by pulse oximeter.

6.4 Follow Up Phase for Patients with Progressive Disease or Who Discontinue Treatment Because of Toxicity or Any Other Reason (other than completing all eligible cycles of pembrolizumab treatment).

These patients will be taken off of pembrolizumab and enter the follow up phase.

Trial Phase	**Safety Follow-up**	**Follow-up**		**Survival Follow-up[1]**
Time from Last pembrolizumab Dose	30 days	3 months	6 months	Starting at 9 months
Visit	Safety Follow up visit	Follow up visit 1	Follow up visit 2	NA
Scheduling Window	+/- 3 days	+/- 7 days	+/- 7 days	+/- 7 days
Administrative Procedures				
Review Medications	X	X	X	
Subsequent Antineoplastic Therapy	X	X	X	X
Survival Status				X
Clinical Procedures/Assessments				
Review Adverse Events	X	X	X	
ECOG Performance Status	X	X	X	
Directed Physical Exam	X	X	X	
Vital Signs and Weight[3]	X	X	X	
Laboratory Procedures/Assessments				
CBC with Differential	X	X	X	
Comprehensive Serum Chemistry Panel	X	X	X	
Patient Reported Outcomes[2]				
EORTC QLQ C-30	X	X	X	
EORTC QLQ-H&N35	X	X	X	

1. During survival follow-up patients should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.
2. The EORTC QLQ C-30 should be completed first.
3. Vital signs to include temperature, pulse, respiratory rate, blood pressure, and oxygen saturation as measured by pulse oximeter.

4.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

Furthermore, additional evaluations/testing may be deemed necessary by the investigator 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 study team must obtain documented consent from each potential subject prior to participating in a clinical trial.

Consent must be documented by the subject's dated signature. 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 Institutional Review Board's (IRB'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 communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the investigator. Details regarding the patients' prior treatment for SCCHN 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 30 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 the patient's SCCHN, including all prior treatments received.

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.

7.1.1.6.4 Patient Reported Outcomes

The EORTC QLQ C-30 and EORTC QLQ-H&N35 questionnaires will be administered by site personnel and completed by subjects at time points shown in the flow charts above. The EORTC QLQ C-30 will be completed first, followed by the EORTC QLQ-H&N35.

7.1.1.6 Assignment of Subject Number

All consented subjects will be given a unique number. The performance site should contact the coordinating center to obtain each subject's unique, sequential number. That number will be used to identify the subject throughout the study. The number will not contain any direct subject identifiers.

7.1.1.7 Trial Compliance (Medication/Diet/Activity/Other)

Administration of trial medication will be documented in the subject's case record. The instructions for preparing and administering pembrolizumab will be provided in the Pharmacy Manual.

Subjects who are unable to comply with protocol requirements (i.e. attend study visits within protocol prescribed windows, complete study assessments, etc.) may be removed from the protocol by the Investigator.

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 Charts and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 12). Toxicities will be characterized in terms of seriousness, causality, toxicity grading and action taken with regard to trial treatment.

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 (irAE). See Section 5.7.2 and the separate guidance document in the study appendices regarding the identification, evaluation and management of AEs of a potential immunological etiology.

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 and at other time points as documented in Section 6. Clinically significant abnormal findings should be recorded.

7.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per Section 6, 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 other time points as specified in Section 6. Vital signs should include temperature, pulse, respiratory rate, blood pressure, pulse oximetry, and weight. 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 12.1) at screening, prior to the administration of each dose of trial treatment and at all other time points as specified in Section 6.0.

7.1.2.6 Tumor Imaging and Assessment of Disease

7.1.2.6.1 Initial Tumor Imaging

Initial tumor imaging must be performed within 28 days prior to the start of radiation and pembrolizumab and at the time points indicated in Section 6.0. A PET/CT scan will be required for initial tumor imaging. CT scan should be a diagnostic CT including CT neck with IV contrast, CT chest with IV contrast, and CT abdomen/pelvis with IV and oral contrast to

adequately rule out metastatic disease. If the investigator feels that MRI will be the best way to follow the patients head and neck disease subsequently, then an MRI of the neck should be done at baseline as well. However, CT scan is encouraged over MRI.

Positron emission tomography (PET) in combination with systemic administration of a glucose analogue, fluorodeoxyglucose (FDG), is an imaging modality that measures metabolic activity of individual tissues. Tissues with large energy requirements, e.g. tumors, incorporate higher levels of FDG than surrounding normal tissue, allowing whole body tumor screening. PET in combination with diagnostic CT is now considered the standard of care in the initial staging and evaluation of treatment response or recurrence in SCCHN at most centers.[77, 78 79] Using a multi- modality PET-CT scanner 3-D functional and anatomic images will be acquired and registered, and fused images will be viewed. A negative PET/CT done at 3 months after completion of treatment with radiation or chemoradiation has been shown to have a very high negative predictive value of 95-100%.[78-82] For example, data at the University of Maryland Medical Center shows PET scan negativity, defined as an SUV of <1.5 compared to surrounding parenchyma, is 100% sensitive for the absence of disease in the post-treatment setting (Wartmann, Submitted).

Standard FDG-PET isotope preparation and scanning techniques will be employed. Regions from the base of the brain to the lower abdomen will be imaged approximately 60 minutes after FDG injection. Primary tumor metabolism will be measured by FDG PET using Standard Uptake Values (SUV). SUVs are determined by examining a specific region of interest (ROI) on the scan defined as the maximum 50% activity contour and measuring radioactivity in this area as an average pixel display value (av). The calculation for SUV is: SUV = av ROI [mCi/mL]/injected radioisotope dose [mCi]/body wt [g].

The investigator must review baseline images to confirm the subject has measurable disease per RECIST 1.1.

A PET/CT done as part of clinical practice prior to screening can be used if it meets the above qualifications and is within the stated time frame.

7.1.2.6.2. Tumor Imaging at 3 Months Post Completion of Radiation

A PET/CT scan will be required for imaging at 3 months post completion of radiation. CT scan should be diagnostic, including CT neck with IV contrast, CT chest with IV contrast, and CT abdomen/pelvis with IV and oral contrast. PET imaging should be completed as discussed in 7.1.2.6.1 above. If MRI neck has been done at baseline and will be the primary modality to follow the patient's head and neck disease, then MRI neck should be done at 3 months as well. CT scan is encouraged over MRI.

7.1.2.6.3 Subsequent Tumor Imaging

Subsequent tumor imaging will be with CT neck with IV contrast. Chest imaging will be with CT chest with IV contrast or chest X-ray PA/lateral as determined by response and time in follow up as detailed in section 6.0. MRI of the neck may be done as the primary means of following the patients' disease if this is determined to be the most accurate study by the investigator. If MRI of the neck will be used, then the CT neck can be omitted. CT scans

are encouraged over MRI. Unless clinically indicated, the same imaging modality (MRI neck or CT neck) should be used throughout the study.

7.1.2.6.4 Assessment of Disease

7.1.2.6.4.1 Definitions

Measurable Lesions: Lesions that can be accurately measured in at least one dimension with longest diameter at least ≥10 mm on CT scan (or >20mm by X-ray). Cystic lesions thought to represent cystic metastasis can be considered as measurable lesions.

Malignant Lymph Nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm when assessed by CT scan.

Non-measurable Lesions: All other lesions < 10 mm or lymph nodes <15mm by CT scan.

Target Lesions: All measurable lesions up to a maximum of 2 lesions per organ and up to 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), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement. In this circumstance, the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

7.1.2.6.4.2 Evaluation of Disease Response

Response determination will be defined based on RECIST 1.1. (Table 8).

Table 8. Definition of Response in Target Lesions.

Response	Definition
Complete Response (CR)	Disappearance of all target lesions*
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions compared to baseline sum of target lesions, or any new lesions
Stable Disease (SD)	Neither sufficient decrease to qualify as a PR or sufficient increase to qualify as PD

*After treatment of SCCHN patients with radiation it may be difficult to distinguish residual disease from treatment effect/normal tissue. This will be a critical consideration at 3 months post completion of radiation. As detailed above PET/CT can play a significant role in determination of residual disease at 3 months post completion of radiation. If a target lesion has decreased in size but has not completely resolved and the lesion is not PET avid (defined as an SUV that is not higher than background soft tissue) then the patient is considered to have a complete response. If a target lesion has decreased in size, but has not completely resolved, and it has any PET activity a biopsy can be done at the discretion of the investigator. If a biopsy done and is negative then the patient will be considered to have a complete response. If the biopsy shows residual malignancy or a biopsy is not done then the patient will be considered to have a partial response or stable disease as determined by RECIST 1.1.

Per RECIST 1.1, response should be confirmed by a repeat CT scan. The scan for confirmation of response may be performed at the earliest 4 weeks after imaging that showed response (if clinically indicated) or at the next scheduled scan.

Lesions that can be measured clinically on physical exam (skin lesions or palpable lymph nodes) will be measured by the investigator with the longest axis recorded. These measurements can be used to guide clinical decision making, for example prompting an earlier CT scan to evaluate disease. However, only measurements based on radiology will be used to determine response.

Table 9. Assessment of Non-Target Lesions

Response	Definition
Complete Response (CR)	Disappearance of all non-target lesions
Incomplete Response/Stable Disease (SD)	Persistence of one or more non-target lesions
Progressive Disease	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail.

7.1.2.6.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence.

Table 10. Best Overall Response

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

Given the observed pattern of response with immunotherapy medications (anti-PD-1 mAb, anti- PD-L1 mAb, and Anti-CTLA4 mAb) where some patients develop evidence of progressive disease by RECIST 1.1, with significant increase in size of target lesions and/or new lesions, followed by regression of disease to SD or PR/CR[2], all imaging showing progressive disease by RECIST 1.1, in the absence of significant clinic deterioration of the patient will be confirmed with a repeat CT scan at least 4 weeks from the initial imaging showing progression. Clinically stable patients will continue treatment in the interim before this scan. If progressive disease is confirmed on subsequent imaging, the patient will be defined as having progressive disease and will be taken off of the study. Progressive disease by RECIST 1.1 with clinical deterioration by the patient will be counted as progressive disease, and study treatment will be discontinued.

Determination of clinical deterioration is at the discretion of the treating physician as defined by progression of disease at critical sites requiring urgent intervention (for example cord compression), or development of signs and symptoms of disease progression and/or significant decline in ECOG performance status.

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

7.1.2.7.1 PD-L1 and p16 Expression in Tumor Samples

PD-L1 expression and p16 status will be correlated with efficacy outcomes retrospectively. Frozen samples, plastic embedded samples, or formalin fixed samples that has been frozen at any point will not be accepted for analysis. Tumor samples that undergo analyses for research purposes will not contain any direct subject identifiers. Samples will be labeled with the participant study ID, tumor site and collection date. A Tissue Block Shipping Form (see protocol appendix) will need to be completed and submitted with each tumor block Tumor samples should be large enough to make about 10 slides. Archival tissue or formalin fixed paraffin embedded tissue should be sent to the Coordinating Center via 2 day shipping that maintains a documented chain of custody (e.g. Fed Ex).

PD-L1Expression

Tumor tissue for PD-L1 analysis from a formalin fixed paraffin embedded (FFPE) fresh biopsy or archival tissue sample of a tumor lesion will be obtained before treatment begins. Tumor tissue will be shipped to the Coordinating Center. The Coordinating Center will send tissue slides to the Merck designated lab for PD-L1 analysis. For archival or fresh biopsies, core needle or incisional/excisional biopsy should be used (fine needle aspiration is inadequate). Fixation time for samples should be 24 hours to 48 hours in 10% neutral buffered formalin. FFPE blocks will be sectioned by the Coordinating Center to make 5 positively charged slides. The same method of slide preparation will be used for archival tissue samples.

"Positive" PD-L1 expression will be defined as >1% of tumor cells with PD-L1 expression. If a biopsy is required after treatment to confirm CR, this sample will also be sent to the Coordinating Center using the method above. The Coordinating Center will send slides to the Merck designated lab for exploratory PD-L1 expression analysis if malignant tissue remains.

p16

Additionally, for patients with oropharyngeal cancer (recurrence or second primary) pre-

treatment tumor tissue (archival or fresh biopsy) will be evaluated for p16 expression by immunohistochemistry at the treating institution.

Other remaining tissue received by the Coordinating Center will be stored in the UPMC Hillman Cancer Center for at least 10 years. If the subject consents to future biomedical research, any leftover tissue(s) will be stored indefinitely at the UPMC Hillman Cancer Center in the Ferris lab.

7.1.2.7.2 Correlative Studies Blood Sampling

For sites participating in correlative studies: Samples of patient's blood will be collected at time points as detailed in Section 6.0. Approximately 2 teaspoons of blood will be drawn into a Na heparin 'green top' tube. The tube will be labeled with the study number (HCC 18-009), patient's study ID number, date and time of blood draw. Samples drawn at the UPMC Hillman Cancer Center should be hand delivered to the Ferris Lab (Research Pavilion Lab 2.19, 5117 Centre Avenue, Pittsburgh, PA 15213) within a half hour of collection. As detailed in section 6.0, blood draws for correlative studies will be drawn prior to dosage of pembrolizumab at first and third cycle, and additionally at week 17 visit and at visit at time of progression.

Blood samples from non-UPMC Hillman Cancer Center performance sites will either be sent unprocessed via courier on the date of collection to the Ferris Lab **OR** they will be processed on site and sent to the Ferris Lab using the instructions below.

For sites doing on-site processing: Samples should be processed by the lab within four hours of blood draw. Once in the lab, blood will be diluted 1:1 with phosphate buffered saline (PBS) and then layered onto an equal volume of Lymphocyte Separation Media. The blood will then be centrifuged at 1500g for 30 minutes (no break) at room temperature within one hour of collection. The plasma will be removed, aliquoted, and labeled with the study number, subject's study number, "plasma", volume and date, and frozen at -80°C. The cells or "buffy coat" will then be removed, and placed into a new 15cc conical tube. Ten ml of ice cold PBS will be added to the cells in the tube and then the tube will be inverted 5 times and centrifuged (brake on) at 350g for 10-15 min at 4°C. The tube will be gently inverted to pour off supernatant—the pellet should not be disturbed. Once the tube is upright the pellet will be dislodged by gently tapping the tube. Ten ml of ice cold phosphate buffered saline (PBS) will be added. The tube will be inverted five times, a 100ul aliquot removed for counting, then centrifuged one last time at 350g for 10-15 min at 4°C. Cells will be counted by trypan blue exclusion. After centrifugation, supernatant will be aspirated and the cells will be re-suspended to yield cells at 10-20 million cells per ml in freezing media (95% FBS / 5%DMSO). The viably frozen cells will be labeled with the study ID, subject's study ID, date and number of cells. The cells should be placed in a Mr. Frosty, if possible, in a -80°C freezer until shipment. If shipment is longer than a few days after collection, transfer to liquid nitrogen or a -150°C freezer. The frozen cells and plasma will be shipped to the Ferris Lab at the UPMC Hillman Cancer Center.

Future Biomedical Research
If a patient consents to future biomedical research, then an additional 2 teaspoons of blood will be drawn at the same time points as detailed in section 6.0, prior to dosage of pembrolizumab at first and third cycle, and additionally at week 17 visit and at visit at time of progression. After drawing blood they will then be processed and labeled as detailed above.

Specimens from non-UPMC Hillman Cancer Center performance sites should be transported via courier or shipped on dry ice via overnight delivery (Monday thru Thursday only) to the following address:

Ferris Lab
UPMC Hillman Cancer Center
Research Pavilion Lab 2.19
5117 Centre Avenue
Pittsburgh, PA 15213
Phone: 412-623-7738

Overnight shipments must be sent Monday through Thursday only.

Please contact the Ferris Lab (412-623-7738; reederc@upmc.edu) at the time of courier transport or shipment.

After completion of the trial, the samples for correlative studies will be thawed. The following lymphocyte phenotypes will be analyzed by flow cytometry: cytotoxic T cells (CD8+CD3+CD28-CD57+), regulatory T cells (CD4+CD25+FOX-P3+) and myeloid derived suppressor cells (CD11b+HLA-DR[-]CD33+). These samples will be analyzed for these cell types to evaluate if there is any correlation with pre-protocol treatment levels of these cells, as well as changes over time and efficacy endpoints. These analyses will be done in the Ferris Lab at the UPMC Hillman Cancer Center.

7.1.3 Laboratory Procedures/Assessments

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Clinical laboratory tests for this trial are specified in Table 11. For these laboratory tests the total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post- trial visits), are all standard of care.

Table 11. 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	PT (INR)
WBC (total and differential)	Aspartate Aminotransferase (AST)	Specific Gravity	aPTT
Red Blood Cell Count	Lactate Dehydrogenase (LDH)	Microscopic Exam *(If abnormal*	Total Thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide	*results are noted)*	Free Tyroxine (T4)
	(CO_2 or biocarbonate)	Urine Pregnancy Test †	Thyroid Stimulating Hormone (TSH)
	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		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

Laboratory tests for screening or entry should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 48 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab will discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.2.1. After discontinuing

treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

7.1.4.2 Blinding/Unblinding

The investigators will not be blinded to the treatment received.

7.1.5 Visit Requirements

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

7.1.5.1 Screening

Within 28 days prior to initiation of treatment, the patient will be evaluated by the study team to determine if the patient is eligible for the trial. Clinical and radiologic tests will be done as per Section 6.0 and are required to be done within 28 (unless otherwise specified in Section 6.0) days of the first dosage of pembrolizumab. Prior tumor imaging can be used if determined to be adequate by the investigator and within time requirements for CT scan and PET/CT as per section 6.0. Because dental evaluation/treatment may be required treatment with radiation as part of standard of care, this evaluation can be started/completed before a patient is consented for the protocol. Laboratory tests for organ function screening (as per inclusion criteria #13) should be performed within 21 days prior to the first dose of treatment. All other required laboratory tests for screening as per section 6.0 can be done within 28 days.

7.1.5.2 Treatment Period

Visit requirements are outlined in Section 6.0. Specific procedure-related details are provided in Section 7.1.

7.1.5.2.1 Retreatment with pembrolizumab

Some patients who discontinue pembrolizumab may be eligible for retreatment with pembrolizumab for up to one year if this study remains open and the patient meets the following criteria:

1. Stopped pembrolizumab after attaining a confirmed CR anytime during the study or had a CR, PR, or SD at time of completion of all 24 months of study treatment.
2. Experienced a recurrence or disease progression on imaging study confirmed by the investigator.
3. Has not been treated for recurrence/disease progression with other anti-cancer treatment.
4. Still meets all inclusion/exclusion criteria (not including criterion that patient is a candidate for reirradiation).

These patients will undergo trial screening procedures as per Section 6.1, with the following exceptions:

- Patients will not have to sign another informed consent document.
- Patients will not require PET/CT, but will require diagnostic CT, including CT neck and chest with IV contrast and CT abdomen/pelvis with IV and oral contrast

(MRI may be done at investigator discretion if previously used).
- Patients will not require repeat biopsy for evaluation of PD-L1 expression.

Patients will undergo serum collection for correlative studies before initiation of retreatment with pembrolizumab. Patients who meet criteria for retreatment will be treated and followed as per Section 6.3.

7.1.5.3 Post Pembrolizumab Treatment Visits

7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of pembrolizumab or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of grade > 1 will be followed until the resolution of the AE to grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

7.1.5.4 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression or withdraw of consent will move into the Follow-Up Phase and should be assessed as per Section 6.2. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section 7.1.5.2.1. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated. If a new anti-neoplastic treatment is initiated during this phase, the patient will then be followed as per Section 6.4.

7.1.5.4.1 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject will be followed per Section 6.4. Starting at 9 months from the last pembrolizumab dose, the patient will move into the survival follow-up phase. In this phase, patients should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.2 Assessing and Recording Adverse Events

7.2.1 Definitions

The following definitions of terms apply to this section:

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

Life-threatening adverse event or *life-threatening suspected adverse reaction:* An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It

does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or *serious suspected adverse reaction:* An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

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

Unexpected adverse event or *unexpected suspected adverse reaction:* An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.2.2 Eliciting AE Information

Research subjects will be routinely questioned about AEs at study visits.

Recording Requirements

All observed or volunteered adverse events (serious or non-serious) and abnormal test findings, regardless of study group or suspected causal relationship to the study drug(s) will be recorded in

the subjects' case histories. For all adverse events, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a *serious adverse event*) and; 2) an assessment of the casual relationship between the adverse event and the study drug(s).

AEs or abnormal test findings felt to be associated with the investigational drug or study treatment(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Sponsor-Investigator.

7.2.3 Abnormal Test Findings

An abnormal test finding will be classified as an *adverse event* if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms.
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy.
    - **Note**: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an AE.
- The test finding leads to a change in study dosing or discontinuation of subject participation in the clinical study.

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

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

7.2.3.1 Definition of an Overdose for This Protocol and Reporting of Overdose to Merck

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by 20% over the prescribed dose. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

If a dose of Merck's product meeting the protocol definition of overdose is taken without

any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety (Attn: Worldwide Product Safety; FAX: 215 993-1220) using the protocol adverse event case report form (CRF). If the protocol adverse event CRF does not contain enough information, Merck may contact the performance site to request additional information.

7.2.3.2 Reporting of Pregnancy and Lactation 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 protocol therapy, 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 pregnancy outcome must also be reported.

Such events must be reported within 24 hours to the Sponsor and faxed within 2 working days to Merck Global Safety (Attn: Worldwide Product Safety; FAX: 215 993-1220) using the protocol adverse event case report form (CRF). If the protocol adverse event CRF does not contain enough information, Merck may contact the performance site to request additional information.

7.2.4 Immediate Reporting of Adverse Events

7.2.4.1 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 12 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.

All events meeting the definition of a serious adverse event should be reported according to the departmental SAE checklist and SAE form. The initial SAE form should be sent to the following within 2 business days of the coordinating center Principal Investigator becoming aware:

1. Dan Zandberg (zandbergdp@upmc.edu)
2. CRSSafetySubmissions@upmc.edu
3. Local Institutional Review Board when reporting requirements are met.

NOTE: non-UPMC Hillman Cancer Center (UPMC HCC) sites should send the SAE to the addresses listed above in #1 and #2. The Coordinating Center (UPMC HCC) will report to Merck Global Safety (Attn: Worldwide Product Safety; Fax: 215-993-1220).

In addition to completing appropriate patient demographic and suspect medication information, the report should include as applicable the following information that is available at the time of report within the Sections B and C of the departmental SAE form:

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

Follow-up reports:
Additional information may be added to a previously submitted report by adding to the original departmental SAE form and submitting it as follow-up or creating supplemental summary information and submitting it as follow-up with the original departmental SAE form.

Non-serious Events of Clinical Interest and any other relevant safety information that does not meet SAE criteria are to be forwarded by the performance site to UPMC HCC (Dan Zandberg (zandbergdp@upmc.edu) and CRSSafetySubmissions@upmc.edu), who will forward to Merck Global Safety (Attn: Worldwide Product Safety; FAX: 215 993-1220) using the applicable study case report form. If the protocol CRF does not contain enough information, Merck may contact the performance site to request additional information.

All subjects with serious adverse events must be followed up for outcome/resolution for at least 90 days after stopping protocol therapy.

7.2.4.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the adverse event case report forms/worksheets and reported within 2 working days to UPMC HCC (Dan Zandberg (zandbergdp@upmc.edu) and CRSSafetySubmissions@upmc.edu), who will forward 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 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.

3. In the event a subject develops any of the following AEs, a detailed narrative of the event should be reported as an ECI to Merck Global Safety within 2 working days of the event:
    - grade ≥ 3 diarrhea
    - grade ≥ 3 colitis
    - grade ≥ 2 pneumonitis
    - grade ≥ 3 hypo- or hyperthyroidism

Potential skin events of clinical interest:

Every attempt should be made by the study team to take photographs of the actual ECI skin lesion or rash as soon as possible. If affected, photographs should be taken of:

- the head (to assess mucosal or eye involvement)
- the trunk and extremities
- a close-up of the skin lesion/rash.

If possible, a ruler should be placed alongside the site of the skin occurrence as a fixed marker of distance.

- The time/date stamp should be set in the 'ON' position for documentation purposes.
- Photographs should be stored with the subject's study records.
- Merck may request copies of photographs.

In addition to the photographs, the following documents from the Merck Pembrolizumab Program Event of Clinical Interest Guidance Document (at the end of the protocol) need to be completed and sent to UPMC HCC (Dan Zandberg (zandbergdp@upmc.edu) and CRSSafetySubmissions@upmc.edu), who will forward to to Merck Global Safety (Attn: Worldwide Product Safety, FAX: 215-993-1220) within 2 business day of the subject's presentation with the dermatologic event:

- Appendix 2—Past Medical History Related to Dermatologic Event
- Appendix 3—Presentation of the Dermatologic Event

- Appendix 4—Focused Skin Examination

A separate guidance document has been provided in the appendix entitled "Event of Clinical Interest and Immune-Related Adverse Event Guidance Document." This document provides guidance regarding identification, evaluation and management of ECIs and irAEs. Additional ECIs are identified in this guidance document and also need to be reported to Merck Global Safety within 2 working days of the event.

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.

ECIs that occur in any subject from the date of first dose through 90 days following cessation of pembrolizumab treatment, or the initiation of a new anticancer therapy (whichever is earlier) whether or not related to pembrolizumab, must be reported to Merck Global Safety within 2 working days.

7.2.5 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), version5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

Table 12. 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 mild 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 the investigational condition 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 exposed to the investigational condition regardless of time to diagnosis);or	
	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 study treatment to be discontinued?	
Relationship to Test Condition	Did the investigational condition cause the adverse event? The determination of the likelihood that the investigational condition caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the investigational condition and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the investigational condition caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the investigational condition 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 investigational condition? Is the time of onset of the AE compatible with a study-induced effect (applies to trials with investigational medicinal product[s])?
	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 Investigational Condition (continued)	**The following components are to be used to assess the relationship between the test condition and the AE: (continued)**	
	Dechallenge	Was the investigational condition 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 investigational condition; or (3) the trial is a single-exposure trial; or (4) The test condition is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the test condition 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 exposure trial); or (3) The test condition 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 INVESTIGATIONAL CONDITION, OR IF REEXPOSURE TO THE INVESTIGATIONAL CONDITION POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE MERCK 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 test condition?
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 test condition relationship).**
Yes, there is a reasonable possibility of test condition relationship.		There is evidence of exposure to the test condition. The temporal sequence of the AE onset relative to the administration of the test condition is reasonable. The AE is more likely explained by the test condition than by another cause.
No, there is not a reasonable possibility of test condition relationship		Subject was not exposed to the test condition OR temporal sequence of the AE onset relative to administration of the test condition is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

7.2.6 Sponsor Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

This study will test the efficacy of reirradiation combined with pembrolizumab, administered at 200mg IV every 3 weeks, in patients with unresectable locoregional recurrence or second primary head and neck squamous cell carcinoma. In addition, the early toxicity profile and safety of the combination of the mAb with radiation therapy will be established.

This is a single-arm phase II trial with continuous monitoring of acute non-hematologic toxicity. The primary efficacy endpoint is Progression-Free Survival (PFS). The efficacy outcome of the study will be summarized by the median time to progression or death. This will be related to experience reported in the literature.

While the safety profile of pembrolizumab is well established when giving the drug as a single agent, the safety of the combination of pembrolizumab with high dose ionizing radiation needs to be established. In case the defined boundary for the incidence of severe non-hematologic toxicity is crossed, the trial will be stopped, and the available data at that point will be carefully reviewed in order to suggest potential modification of the drug-radiation combination that may warrant testing in a future, independent trial.

8.2 Statistical Analysis Plan

The design includes 1) continuous toxicity monitoring in the first 20 patients enrolled and 2) evaluation of toxicity and efficacy after the pre-specified target sample size is reached and the efficacy data have matured.

8.2.1. Continuous Toxicity Monitoring in the First 20 Patients Enrolled (Stopping rule)

The endpoint is severe (grade 4-5), non-hematologic toxicity that occurs during the radiation therapy plus 2 weeks (i.e. within the first 7 weeks of trial treatment). Based on the literature review, grade 4-5 acute radiation toxicity occurs in <20% of radiation-drug combinations tried in the reirradiation setting for SCCHN. Early stopping for unexpected, severe toxicity is based on continuous monitoring of grade 4-5 non-hematologic toxicity with the aim of keeping the probability of early stopping at around 5% if the true underlying rate of this toxicity is 20%. Following Ivanova et al. [83] we use the boundary proposed by Pocock. [84] If $\geq b_k$ patients with toxicity have been observed after enrolling the first k patients, then the study will be stopped as detailed above. Values of b_k for the current design are given in Table 13.

Table 13. Pocock boundary for early stopping due to excessive grade 4+ toxicity with a probability of stopping of about $\phi = 0.05$ and assuming the true toxicity rate is $\theta_0 = 0.2$

k	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
b_k	–	–	3	4	4	4	5	5	5	6	6	6	7	7	7	8	8	8	9	9

It is important for the validity and practical implementation of this strategy that the sequence of patients entered into the study is strictly recorded and preserved. Ideally, the design assumes that the outcome, i.e. the incidence of grade 4+ toxicity among the first *i* patients is known when entering patient *i+1*. However, the accrual rate is expected to be around two patients per month, and the time window for observing early toxicity in a patient is pragmatically defined as the time during and within two weeks after the completion of RT. Therefore, insisting on complete observations before entering the next patient will slow down accrual considerably. Instead we will allow staggered entry of cases. For patient safety reasons, no more than 5 patients will be allowed to be undergoing or be within 2 weeks of completing reirradiation treatment at any point during the enrollment of the first 20 patients.

At the time when the boundary is crossed, the treatment with pembrolizumab will be discontinued in all patients on treatment at that point in time and toxicity data will be reviewed by the DSMB (Data and Safety Monitoring Board).

If 20 patients are enrolled and have completed therapy (radiation plus 2 weeks) without crossing the toxicity boundary, toxicity data from those patients will be reported and reviewed by the DSMB. No further accrual will occur until after DSMB review. All subsequent accrual will be continued with respect to the efficacy question and although there will be no further toxicity boundary halting the study, toxicity will still be recorded and reported for the whole phase II cohort.

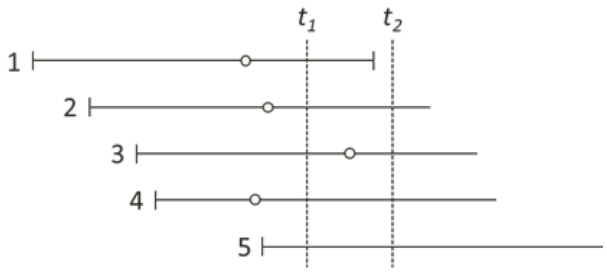


Fig. 1. Hypothetical example of the timeline for enrolling and recording toxicity in the first 5 patients. At time t_1, 2 of the first 3 patients have developed grade 4+ toxicity and the trial should continue. At this point in time 3/4 and 3/5 patients have developed relevant toxicity and the boundary for stopping accrual at this dose level is still not crossed. At time t_2, 4 of the first 4 patients enrolled have developed grade 4+ toxicity which means accrual should stop at this point in time. The status of the 5^{th} patient at time t_2 does not affect the decision as to whether the boundary is crossed or not.

An impression of the statistical power of the initial continuous toxicity monitoring phase may be achieved from a specific example. If 2 out of 20 patients develop grade 4+ early toxicity, the estimated incidence is 10%, and the upper limit of the exact 1-sided 95% confidence interval is 28%.

8.2.2 Primary Efficacy Analysis

All patients entered are evaluable with respect to the efficacy endpoint, which is the main trial endpoint. The primary endpoint is progression-free survival (PFS). Based on the literature review presented in the background section, we assume that reirradiation without pembrolizumab produces a median PFS of 8 months.

The expected accrual rate is 2 patients per month for a total of 48 evaluable patients. A 12-month maturation period after completing accrual has been added. All patients will be included in efficacy analysis irrespective of the dose of drug or radiation actually received. This follows a strict intention-to-treat principle. Subjects eligible for replacement are discussed in section 5.10. We will use a 1-sided test with a 5% significance level (α) to test the uni-directional hypothesis that the median PFS is prolonged from 8 to 12 months by combining anti-PD-1 mAb with reirradiation. We estimate that the power (1-β) of the study is 78%. The efficacy result will be summarized as a median PFS with a 1-sided 95% confidence interval. No early stopping rule for futility is planned due to the relatively rapid enrollment of patient in relation to the expected median PFS.

8.2.3 Efficacy

Endpoints Primary

Progression-free survival (PFS) – Progression free survival is defined as the time from the initiation of treatment to the first documented disease progression per RECIST 1.1 or death due to any cause, whichever occurs first. If a patient recurs and is eligible for retreatment, then only the time to the initial recurrence will be included in the evaluation of PFS. Patients who are alive with no evidence of disease at the time of last contact will be censored at that date.

Secondary

Overall Response Rate (ORR) – The overall response rate is defined as the percentage of the patients who have a complete response (CR) or partial response (PR) as defined by RECIST 1.1. The patient's best overall response rate defined as the best response recorded from the start of the treatment until disease progression will be recorded.

Clinical Benefit Rate (CBR) - Clinical benefit rate is the percentage of patients that have achieved a complete response, partial response, and stable disease as defined by RECIST 1.1.

Time to in-field progression – The time to in-field progression is defined as the time from initiation of treatment to progression of disease within the radiation field.

Overall Survival – Overall survival is defined as the time from first treatment until death. Patients who are alive will be censored at the last date of patient contact.

8.2.4. Biostatistical considerations in relation to proton therapy

For the primary toxicity and efficacy analyses, toxicity and efficacy outcomes will be recorded and analyzed without stratification for radiation modality. While proton has some unique

qualities compared to photon (described in section 4.2.2.2), currently, there has not been a direct prospective comparison of photon and proton radiation, and therefore it is not known whether there is any difference in efficacy, toxicity, or immunogenicity between photons and protons in reirradiation of HNSCC. Therefore, pre-specified stratification is not required. Proton is also not an experimental treatment itself and therefore it does not need to be added as an additional experimental arm in this trial.

In regards to the continuous toxicity evaluation (section 8.2.1 above) It is expected that early grade 4+ radiation toxicity will generally be observed in the high-dose region where radiation is given to gross disease. It should be noted that as described in section 4.2.2.2 above, the main difference between proton and photon is the dose to normal tissue rather than the high dose to the target volume ie high-dose region. However, in order to add extra safeguards with proton therapy, when 5 proton patients have been accrued and pass the 7 week mark on trial, the DSMB will review the data at that time and compare toxicity of proton patients to photon patients, to determine if further proton therapy should be allowed. The trial will continue to enroll photon patients during that review however proton patients will not be allowed until after the DSMB review. If the first 5 patients are enrolled before a total of 20 patients have gone past week 7, then after this review of the proton patients, the trial will continue to accrue to the 20 initial patients as described above, with subsequent DSMB review either when the toxicity threshold is crossed or when 20 total patents (includes proton and photon) have gone past the 7 week mark. If the toxicity boundary is crossed, the independent DMSB will be charged with reviewing the data including whether there is any statistical reason to believe that the incidence of grade 4+ toxicities is less or more in the proton therapy cases. If this should be the case, the DMSB may advise as to whether only photon or only proton patients should continue accrual. Similarly, when the 20 patients pass week 7 if the toxicity threshold is not met the DSMB will again evaluate toxicity for proton vs. photon patients.

If the first 5 proton patients are not accrued until after the first 20 patients, then similarly when 5 patients are accrued the DSMB will evaluate the data compared to photon to make a decision as to whether the option of proton therapy should still be allowed.

In regards to the efficacy questions, the main hypothesis is that radiation will be synergistic with pembrolizumab because of the immunogenic effect of radiation detailed prior in the protocol.

Proton radiotherapy induced cell death is the same mechanism as in photon radiation. Therefore, we would not expect a different effect on the target volume. There is a hypothetical difference in that less normal tissue exposure from proton may lead to less killing of lymphocytes and thus might be hypothetically more immunogenic than IMRT. However, this is only hypothetical, and it is unclear if this plays a significant role in the immunogenic effects of radiation in humans.
Therefore, we assume that there is no effect of radiation modality on efficacy. The primary efficacy analysis will therefore not have a pre-specified stratification for radiation modality, nor is the study powered to allow for any formal comparison between radiation modalities.

However, provided that at least 10 patients each are treated with protons and photons, in addition to analyzing the entire cohort of patients, the toxicity profile and efficacy data will be retrospectively analyzed by radiation modality.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The performance site principal 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.

Pembrolizumab will be provided to the performance sites by Merck as summarized in Table 13. Sites will complete the Drug Request Form (provided as a document separate from this protocol), and send via email to Senthooran Selvarajah (senthooran.selvarajah@merck.com) and Tammy Moll (tammy.moll@merck.com).

Table 13. Product Description

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

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount administered to 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 Compliance with Laws and Guidances

This study will be conducted in accordance with current U.S. Food and Drug Administration (FDA) Regulations, Good Clinical Practices (GCPs) and International Counsel on Harmonization (ICH) E6 Guidelines.

10.1.1 Institutional Review Board (IRB)

Site specific documents (e.g. HIPAA authorization, consent form, advertisements) should be submitted to the Coordinating Center for review and approval prior to IRB submission. The protocol and related study documents will be sent to the performance site IRB for review and approval per local practice. Study procedures may begin at the site once local IRB approval is secured and other details (e.g. study supplies, clinical trial agreements) are in place. All amendments, instances of reportable new information (i.e. unanticipated problems, data breaches, etc.) and continuing review reports will be submitted to the performance site IRB per local practices. All site specific IRB approved documents (e.g. consent, advertisement) and IRB approval letters should be forwarded to the Coordinating Center.

10.1.2 Clinical Trial Monitoring

Data safety and verification monitoring will be conducted in accordance with the UPMC Hillman Cancer Center SOP HCC- CC-CRS-CLIN-027, the Code of Federal Regulations (CFR), and FDA and International Counsel on Harmonization (ICH) E6 Guidelines.

10.1.3 Data Safety and Monitoring Plan

Investigator/Sub-investigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet regularly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, the following:

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

Minutes from the disease center DSMB meetings are available to those who are unable to attend in person.

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

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

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

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

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

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

10.1.4 Records Retention

Essential documents should be retained by performance sites until notification is received from the Coordinating Center that the documents may be destroyed. In general, documents should be maintained at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records may be maintained in secure offsite storage after completion of study follow-up and data analysis. Performance sites should notify the Coordinating Center in writing of the new document location when documents are

transferred off site.

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

10.3 Data Management
Clinical data will be entered into the OnCore® database by the designated performance site personnel. Information can be entered into Oncore® in a way that is 21CRF11.10 (electronic medical records) compliant. OnCore® is equipped for HIPAA-compliant internet-based entry of protocol tracking and review information.

All study data will be collected by the research team at each and every study visit and recorded in the research record. This data will then be entered in to the OnCore® study database.

All source documents will be obtained and retained along with any study forms,
and placed into the patient's research record.

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12.0 APPENDICES

12.1 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.	

12.2 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).

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

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

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

12.4 Tissue Block Shipping Form

Protocol: A Phase II trial of reirradiation combined with open label Pembrolizumab in patients with locoregional inoperable recurrence or second primary squamous cell carcinoma of the head and neck (SCCHN)

Please complete one form for each tumor block. Include a copy of the pathology report.

Subject Study ID:_____

Date of Tumor Tissue Collection:_____

FFPE Date of Fixation:_____

Length of Fixation in Hours:_____

Anatomical Location:_____

Tumor Site (circle one): Primary Metastatic

Shipment Tracking Number:_____

Send tumor block to the Coordinating Center ATTN: Carly Reeder
UPMC Hillman Cancer Center
Research Pavilion Lab 2.19
5117 Centre Avenue
Pittsburgh, PA 15213
Phone: 412-623-7738