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STUDY TITLE: A Phase II Study of the Addition of Pembrolizumab to Postoperative Radiotherapy in Resected High Risk Cutaneous Squamous Cell Cancer of the Head and Neck

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1.0 TRIAL SUMMARY

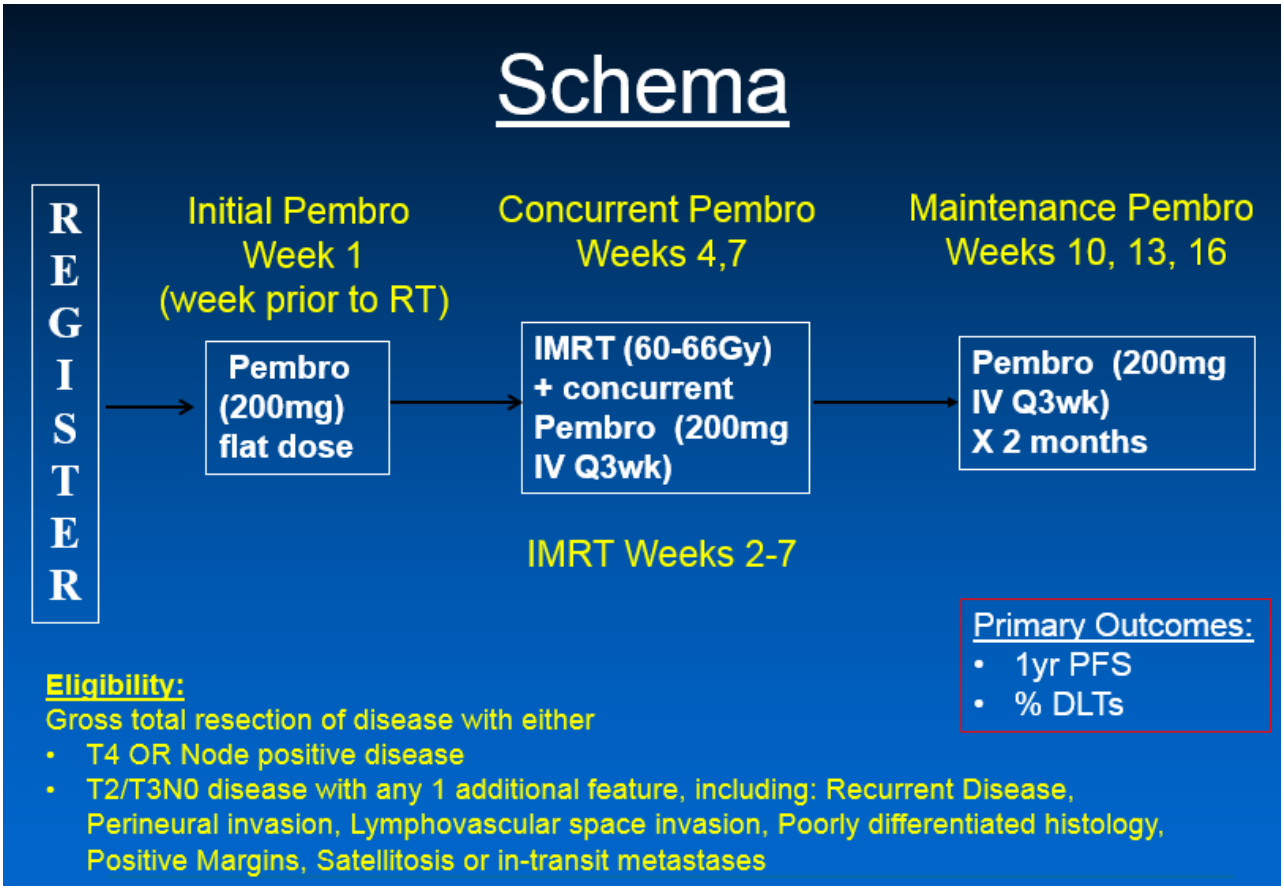
Protocol Number/Title	CASE 6316 A Phase II Study of the Addition of Pembrolizumab to Postoperative Radiotherapy in Resected High Risk Cutaneous Squamous Cell Cancer of the Head and Neck
Study Phase	II
Brief Background/Rationale	While outcomes in resected cutaneous squamous carcinomas are typically very favorable, a subset of high risk resected cancers in the head and neck have a more aggressive disease course despite the routine use of adjuvant radiotherapy. This trial is a treatment intensification protocol which seeks to establish the safety and efficacy of concurrent and adjuvant Pembrolizumab in combination with radiation in the adjuvant treatment of high risk cutaneous squamous cell cancer of the head and neck.
Primary Objective	To assess safety (% of DLTs) and estimate 1-year PFS of postoperative RT + concurrent and adjuvant Pembrolizumab in high risk resected cSCC-HN.
Secondary Objective(s)	Patterns of Failure
Correlative Objective(s)	1) To evaluate the relationship of baseline PD-L1 expression by tumor and tumor-infiltrating lymphocytes (TILs) to preliminary efficacy. 2) To phenotype tumor infiltrating lymphocytes and peripheral blood lymphocytes (PBLs), and investigate tumor suppressor populations including Tregs, MDSCs and CD8 suppressor cells and assess ex vivo for effector function by cytokine production and cytotoxicity assays as well as suppressor function in assays with autologous PBLs. 3) To evaluate the tumor microenvironment (TME), and immune markers at the invasive margin of the tumor, including CD8, PD-1, PD-L1, TIM-3, galectin-9 or HMGB-1, BTLA and HVEM, as well as Lag-3, CTLA-4 and others. 4) To evaluate the genomic and/or transcriptomic profile of these tumors using RNA-seq /Whole Transcriptome Shotgun Sequencing
Sample Size	37 participants Age >18, Male and females eligible
Disease sites/Conditions	Skin cancer of the head and neck (squamous)
Interventions	IMRT 60-66Gy over 6 weeks
	Pembrolizumab every 3 weeks for 16 weeks (6 doses)

2.0 TRIAL DESIGN

2.1 Trial Design

- This is a phase II trial evaluating the addition of concurrent and adjuvant fixed-dose pembrolizumab in combination with standard IMRT, in order to establish safety and estimate efficacy of this regimen to be tested in a subsequent randomized registration trial. Thirty seven patients will be enrolled.
- The primary safety endpoint will be proportion of DLTs. The primary efficacy endpoint will be 1-year PFS. The primary signal to move forward with a subsequent confirmatory randomized study will be a ≤24% overall DLT rate and a favorable 1yr PFS estimate compared to historical controls.

2.2 Trial Diagram



3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** To assess safety and estimate 1-year PFS of postoperative RT + concurrent and adjuvant Pembrolizumab in high risk resected cSCC-HN.

Hypothesis: The addition of concurrent and adjuvant Pembrolizumab to postoperative RT in high risk cutaneous SCC will be safe and yield favorable 1yr PFS results.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**:

5) To evaluate the relationship of baseline PD-L1 expression by tumor and tumor-infiltrating lymphocytes (TILs) to preliminary efficacy .

6) To phenotype tumor infiltrating lymphocytes and peripheral blood lymphocytes (PBLs), and investigate tumor suppressor populations including Tregs, MDSCs and CD8 suppressor

cells and assess ex vivo for effector function by cytokine production and cytotoxicity assays as well as suppressor function in assays with autologous PBLs.

7) For those participants for whom tumor tissue is available, we will evaluate the tumor microenvironment (TME), and immune markers at the invasive margin of the tumor, including CD8, PD-1, PD-L1, TIM-3, galectin-9 or HMGB-1, BTLA and HVEM, as well as Lag-3, CTLA-4 and others.
8) If sufficient tumor is available, we will also evaluate the genomic and/or transcriptomic profile of a subset of tumors using RNA-seq /Whole Transcriptome Shotgun Sequencing

Hypotheses:

1) Baseline PD-L1 expression will not be associated with 1yr PFS.
2) Peripheral immune profiles on PBMC will dynamically change from baseline through treatment and after completion of therapy and correlate with 1yr PFS.
3) Changes in the TME at the marginal edge of the tumor will correlate with 1yr PFS and be marker dependent.
4) Baseline genomic/proteomic tumor profiles will correlate with 1yr PFS

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved.

PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors . Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

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

4.1.2 **Preclinical and Clinical Trial Data**

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

4.2 **Rationale**

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

Disease Background:

Cutaneous squamous cell cancer (cSCC) is the second most common cancer in the U.S. with an estimated incidence of over 700,000 people annually.[1] While most are highly curable with surgery alone, there is a well-recognized subset of patients who demonstrate an aggressive clinical phenotype marked by locoregional recurrence and/or distant metastatic spread. These patients are overwhelmingly comprised of cSCC of the head and neck (cSCC-HN), and frequently demonstrate high risk features including large T3/4 tumors, nodal involvement, lymphovascular space invasion, perineural invasion, and multiply recurrent disease.[2] In a recent population based study, as many as 5,600 patients were estimated to develop nodal metastases and up to 8,700 deaths were attributable to cSCC.[1] Postoperative radiotherapy has been shown in a number of studies to reduce locoregional recurrence and in some studies improve overall survival in this disease.[3-6] However, there are currently no randomized data supporting the use of systemic therapy concurrently and/or adjuvantly to RT, and significant failure rates, both locoregionally and distantly, underscore the limited treatment options for these patients and the need for intensification strategies in addition to RT.

While radiation is typically a highly effective treatment for both cutaneous and mucosal SCC of the head and neck, a mechanism of radioresistance that is becoming increasingly clarified is the tumor microenvironment altering and inhibiting the innate immune response of the host. As a result of recruitment of inhibitory immune cells (e.g. Tregs; activated macrophages), T-cell activation is suppressed and treatment resistance emerges. PD-1 is expressed by multiple immune cells (e.g. cytotoxic T cells, NK cells, dendritic cells) and when coupled with its ligands PD-L1 and PD-L2, the complex promotes "immune escape" in a number of cancers. [7 7, 13, 14] In mucosal head and neck cancer specifically, PD-L1 expression is common, and has been demonstrably linked to the immune-privileged, invasive front of HPV + SCC.[8,9] A recently completed Phase Ib/II study in mucosal head and neck cancer supported this hypothesis as Pembrolizumab, a high-affinity IgG4 mAb which blocks the interaction of PD-1 with both PD-L1 and PD-L2, produced impressive response rates (20% by RECIST criteria) in heavily pretreated recurrent/metastatic patients.[10]

Cutaneous SCC of the head and neck shares many parallels with mucosal SCC as they are both considered to be more prevalent in "immune-weakened" states. While mucosal disease demonstrates

defective antigen presenting cells (APC), and quantitative and qualitative T lymphocyte deficiencies, skin cancer is a disease of aging as older, less robust immune systems become less effective at preventing sun damaged mutated skin cells from cancerization.[11,12] There is early emerging work implicating PD-1 in particular in cutaneous SCC pathways. A recent study demonstrated that immune neutralization of PD-1$^+$ cells resulted in decreased papilloma incidence in mice which was associated with CD4$^+$ and CD8$^+$ T cell infiltrates, as well as increased interferon-γ and decreased transforming growth factor-β production within tumors, supporting the role of PD-1 blockade in SCCS.[13] Another study associates a higher incidence of seropositivity to particular strains of papillomavirus in organ transplant patients as a potential mechanism for the increased incidence in cSCC in these patients, highlighting an important potential overlap between cSCC-HN and mucosal head and neck cancer, known to be frequently HPV induced.[14]

Radiotherapy induces immune responses by releasing tumor antigen, recruiting chemokines and making cells more vulnerable to T-cell killing.[15] PD-L1 upregulation following RT in the tumor microenvironment has been recently demonstrated, and inhibiting its activity using anti-PD-L1 treatment enhanced the effectiveness of RT via a cytotoxic T-cell dependent mechanism.[16] A recent landmark study in melanoma analyzed samples from 46 patients treated with Pembrolizumab and found that tumor regression after therapeutic PD-1 blockade required pre-existing CD8(+) T cells that are negatively regulated by PD-1/PD-L1-mediated adaptive immune resistance.[17] This emerging picture of the importance of the immune response in general, and the PD-1 pathway in particular, being highly associated with carcinogenesis and response to RT provides a sound basis to pursue PD-1 blockade in high risk cSCC-HN.

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

An open-label Phase I trial (Protocol 001) was conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

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

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

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

Recent in vitro studies have demonstrated enhanced radiosensitization with the administration of Pembrolizumab prior to the initiation of radiotherapy (Personal communication: Robert Ferris MD, PhD). As such, the initial dose of Pembrolizumab will be given in this study the week prior to the beginning of IMRT. This is consistent with other trials investigating the combination of PD-1 inhibitors and RT being done in the cooperative group setting. A pilot study that investigated the safety of adding Pembrolizumab to head and neck IMRT in addition to weekly cisplatin was recently presented at ASCO 2017. Powell, et al reported excellent safety profile of 27 patients with locally advanced head and neck cancer treated with chemoradiation with weekly cisplatin, and 70Gy in 35 fractions of IMRT along ith Pembrolizumab 200mg fixed dose IV every 3 weeks beginning 4-7 days prior to the initiation of radiation 2 doses concomitant with IMRT and 5 additional doses post IMRT. 21 patients (78%) completed all planned doses of Pembrolizumab. 3 discontinued due to irAEs (G2 peripheral motor neuropathy, G3 AST elevation, G1 Lhermitte-like syndrome). 3 discontinued due to protocol reasons (early neck dissection -2 pts, prolonged hospitalization-1 pt). All pts completed the full radiation dose (70 Gy) without significant delay (defined as > 5 days). 23 (85%) received the goal target dose of cisplatin (≥200 mg/m2). There was one patient death due to concurrent illness, unrelated to treatment.[18] Based on these results, the NRG Oncology HN-003 study which was designed as a phase I safety study of the addition of Pembrolizumab to postoperative head and neck IMRT and weekly cisplatin discontinued their planned phase I safety study and converted to an open label efficacy signal study. We therefore feel quite confident in the safety of our proposed regimen as our study involves less extensive IMRT fields and does not include any concurrent chemotherapy. We will however monitor DLTs very carefully and include that as a co-primary endpoint of the study.

4.2.3 **Rationale for Endpoints**

4.2.3.1 Efficacy Endpoints

1yr PFS in this patient cohort is suboptimal, and an important measure of disease control.

4.2.3.2 Safety Endpoints

The primary safety endpoints for this study will be dose limiting toxicity (DLT). DLT for this study is defined as the occurrence of a severe adverse event (AE) listed below that is *at least possibly*

related to pembrolizumab, and occurs from the initiation of treatment thru 30 days after the final administration of the study treatment. AEs will be graded according to NCI CTCAE version 4.0.
At the completion of the study, a total DLT rate will be assessed. A DLT rate of ≤24% will be deemed acceptable and if met, the regimen will be deemed appropriate for future study in randomized studies.
The following events will be considered a DLT:

- Any ≥ Grade 3 immune-related toxicity (including graft rejection), except:
    - Grade 3 dermatologic toxicity resolving to Grade 1 or lower with < 2 weeks of systemic immunosuppression
- Any ≥ Grade 3 non hematologic toxicity **except**:
    - Grade 3 in-field radiation dermatitis for which IMRT is not held or held ≤ 1 week (5 fractions)
    - Grade 3 mucositis for which IMRT is not held or is held ≤ 1 week (5 fractions)
    - Asymptomatic Grade 3-4 hypomagnesemia or hypokalemia
    - Grade 3 fatigue
    - Grade 3 dysphagia or feeding tube use
    - Grade 3 weight loss
    - Grade 3 pain
- Grade 3 neutropenia with fever (oral temperature > 39°C)
- Grade 3 thrombocytopenia with bleeding
- Grade 4 neutropenia with/without fever, requiring antibiotics
- Grade 4 thrombocytopenia
- Toxicity of any grade that results in inability to complete IMRT within 8 weeks

4.2.3.3 Rationale for Correlative Endpoints/Biomarker Research

Central hypothesis: Cutaneous squamous cell carcinoma (CSCC) is responsive to combination of PD-1 inhibition and radiation therapy.
To test our hypothesis correlatively we propose the following aims:

Aim 1. To correlate baseline PD-1 expression in the tumor with disease related outcomes.

Rationale: It is unknown whether patients with tumors that express higher levels of PD-1 preferentially respond compared to those that do not. As such, this will be systematically evaluated on all patients.

Research Plan: FFPE tissue blocks will be collected from patients and slides will be cut for subsequent biomarker staining. Analysis of PD-L1 expression will be performed by immunohistochemical staining using the Merck assay. Either complete circumferential or partial linear plasma membrane staining will constitute positive PD-L1 staining. A cut-off of ≥ 5% tumor cell membrane staining will be reported as positive.

Aim 2. To define response to radiation/PD-1 inhibition based on tumor microenvironment and peripheral blood alterations in patients with CSCC.

Rationale: Many solid tumors do respond to checkpoint inhibitors. Little is known in regards to CSCC patients who will or will not respond to the proposed treatment regimen of post-operative radiation and anti-PD-1 therapy.

Research Plan: Prospectively we will stratify study patients into two groups: those that do, or do not respond to the proposed therapy based on historical published data from our institution. The following are the proposed assays for evaluation.

A. Peripheral Blood Lymphocytes

Flow cytometry: Peripheral blood samples drawn from patients pretreatment and at specified times post treatment will be isolated by centrifugation. Surface biomarker expression will be assessed by FACS similar to the analysis of tumor-resident lymphocytes. Staining will evaluate CD3, CD4, CD8 expression as well as cytotoxic markers (perforin, FasL, Granzyme A&B, markers of dysfunction/exhaustion (PD-1, TIM-3, Lag-3), and markers characteristic of regulatory cells (Foxp3, CD25, GITR, CD27, CD28) and markers for myeloid derived suppressor cells. Finally, we will assess TCR clonal diversity using PCR methods.

B. Tissue

Patients for whom fresh tissue is available (e.g. if they consented to other tissue banking IRB approved protocols such as IRB 3164 or 15-1580) or for whom FFPE is available, may have some or all of the following additional correlative studies performed, depending on tissue availability. These include:

Immunohistochemistry: Tumor tissues will be stained and evaluated for indicators of inflammation including the relative degree of lymphocyte infiltration and characterization of immune populations via expression of CD3, CD4, and CD8, as well as the expression of various regulatory-associated markers including PD-1, PDL-1, and galectin-9.

Flow cytometry: tumor tissue will be disassociated by digestion with collagenase/hyaluronidase, prior to FACS analysis of immune population phenotype including CD3, CD4, CD8, and the following cytotoxic markers: perforin, FasL, Granzyme. Studies will also evaluate markers of dysfunction/exhaustion including PD-1, TIM-3, Lag-3, TIGIT and markers associated with regulatory cells/suppression including Foxp3, GITR, CD25, CD27, and CD28 and markers for myeloid derived suppressor cells. Finally, we will assess TCR clonal diversity using PCR methods.

Cytoxicity assays: Tumor resident CD3+CD8+ T cells will be purified by FACS sorting and functionally evaluated for recognition of autologous SCCA and/or general functional ability. Readouts will include proliferation (CFSE dilution, 3-H thymidine incorporation), cytotoxicity (51-Cr release, CD107a staining), and production of interferon gamma and IL-2.

Gene expression analysis: Tumor tissue specimens will be checked by a pathologist to ensure that each contains at least 60% tumor content. Total RNA will then be isolated from 30 to 60 mg of snap-frozen tissue followed by purification of mRNA. Isolated mRNA will then be used to construct a library using the non-stranded TruSeqs protocol, which will then be subjected to high-throughput shotgun sequencing using the Illumina HiSeq 2500 platform by the Case Western Reserve University Genomics Core. Data analysis of transcription profiles will be done in association with the CWRU Genomics Core and correlated with treatment outcome and overall survival data.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Subject Inclusion Criteria

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

1) Histologic diagnosis of cutaneous squamous cell carcinoma of the head and neck that has been resected with no evidence of gross residual disease (margin positivity is acceptable).
2) Patients must have undergone resection of the disease and demonstrate high risk pathologic features including:

- Invasion of the axial skeleton or skull base or skull base foramina
- Node positive disease
- Tumor greater than 2cm with any 1 additional feature, including:
    - Recurrent Disease
    - Perineural invasion
    - Lymphovascular space invasion
    - Poorly differentiated histology
    - Positive Margins
    - Satellitosis or in-transit metastases

- Note: Not all patients with tumors >2cm with one additional risk factor may be ideal candidates for this study, such as patients with only focal perineural invasion without other adverse features. Clinical judgment should be used by the investigator in carefully selecting patients believed to be at significant risk of recurrence with radiation alone.

3) Patients are required to have CT neck and chest or PET/CT and have no documented evidence of distant metastases

4) Patients must not have a history of the following immunosuppressive conditions: bone marrow transplantation and/or organ transplants and/or chronic rheumatic conditions that require active immunosuppressive therapy. Patients with a history of chronic lymphoid or leukemic malignancies which are not under active therapy (no active therapy within the last 3 months) will be eligible. Patients with chronic lymphoid or leukemic malignancies are eligible with or without active disease as long as they have not had treatment within the past three months.

5) Patients may not have had prior therapy with a checkpoint inhibitor (e.g. anti-CTLA-4, anti-PD-1 or anti-PD-L1 therapy);

6) Patients may not have had prior radiotherapy (>30Gy) to the area requiring treatment that would result in any overlap of tissue in both fields

7) Patients may have received chemotherapy or radiation for a previous, curatively treated malignancy provided at least 2 years have elapsed and there is no current evidence of disease (patients with previous or concurrent additional skin cancers will be eligible). Patients with chronic lymphoid or leukemic malignancies are eligible with or without active disease as long as they have not had treatment within the past three months.

8) Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1

9) Age ≥ 18

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

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

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

13) Patients must have adequate laboratory values as per Table 1.

Table 1 Adequate Organ Function Laboratory Values

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

Albumin	≥2.5 mg/dL
[a]Creatinine clearance should be calculated per institutional standard.	

5.1.2 **Subject Exclusion Criteria**

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

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
2. Has a known history of active TB (Bacillus Tuberculosis)
3. Hypersensitivity to pembrolizumab.
4. Has a history of the following immunosuppressive conditions: bone marrow transplantation, and/or organ transplants and/or chronic rheumatic conditions that require active immunosuppressive therapy. Patients with chronic lymphoid/leukemic malignancies that have undergone treatment in the last 3 months will be ineligible.
5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
6. Has had prior chemotherapy, targeted small molecule therapy, or radiotherapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.
    - Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and qualify for the study.
    - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or a separate primary squamous cell carcinoma of the skin. Patients with chronic lymphoid or leukemic malignancies are eligible with or without active disease as long as they have not had treatment within the past three months.
8. Has metastatic disease.

9. Has known history of, or any evidence of active, non-infectious pneumonitis.
10. Has an active infection requiring systemic therapy.
11. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
12. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
13. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
14. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
15. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
16. Has received a live vaccine within 30 days of planned start of study therapy.

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

5.2 **Trial Treatments**

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

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg flat dose	Q3W	IV infusion	Week 1, 4, 7, 10, 13, 16	Experimental
IMRT	60-66Gy	5 days/wk	NA	Wks 2-7 for 30 treatments	Standard of Care

5.2.1 **Dose Selection/Modification**

5.2.1.1 Dose Selection

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

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

5.2.1.2 Dose Modification

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.6.1 and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids. There are no dose reductions for pembrolizumab. If the subject meets retreatment criteria, the full dose of 200 mg will be administered. If subjects do not meet retreatment criteria, then the dose of pembrolizumab will be SKIPPED.

Table 3

Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
			or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism	2-4	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[1]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

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

[1] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose. Note: Pembrolizumab does **not** need to be held for grade 3 dysphagia, grade 3 pain, grade 3 weight loss, or grade 3 fatigue, which are expected toxicities for head and neck radiation and will be managed aggressively by treating investigators per standards of care.

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

5.2.2 **Timing of Dose Administration**

The first dose of Pemrbolizumab should be administered week 1, the week prior to the beginning of radiotherapy (5-10 days preRT is acceptable). RT will begin the week after the initial infusion of Pembrolizumab, typically on a Monday or Tuesday. Trial treatment should be administered as per the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after

the scheduled Day 1 of each cycle due to administrative reasons. All trial treatments will be administered on an outpatient basis.

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

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

5.2.3 **Trial Blinding/Masking**

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

5.3 **Randomization or Treatment Allocation**

All patients will receive IMRT and Pembrolizumab as described above.

5.4 **Stratification**

This is a phase II trial evaluating the addition of concurrent and adjuvant fixed-dose pembrolizumab in combination with standard IMRT, in order to establish safety and estimate efficacy of this regimen to be tested in a subsequent randomized registration trial. Thirty seven patients will accrued. The primary safety endpoint will be proportion of DLTs. The primary efficacy endpoint will be 1-year PFS. The primary signal to move forward with a subsequent confirmatory randomized study will be a ≤20% overall DLT rate and a favorable 1yr PFS compared to historical controls.

5.5 **Concomitant Medications/Vaccinations (allowed & prohibited)**

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

5.5.1 **Acceptable Concomitant Medications**

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

the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

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

5.5.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below and in greater detail in the ECI guidance document. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as

symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

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

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/Colitis**:

  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
    - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
    - For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.

- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

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

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

- **Hypophysitis**:

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

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

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.

        - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
    - **Grade 3-4** hyperthyroidism
        - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

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

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

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

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

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
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	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
(e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	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.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

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

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

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

5.7.3 **Use in Pregnancy**

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

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

5.7.4 **Use in Nursing Women**

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

5.8 **IMRT**

IMRT will be delivered in 30 fractions over 6 weeks (five fractions per non-holiday week) in one plan (SIB) to a total dose of 60-66Gy. Missed treatments due to holidays or logistic reasons can be compensated for by delivering an additional BID treatment during the week, OR treating on the Saturday or Sunday of that week, OR adding to the end of treatment.

5.8.1 **Immobilization and Simulation**

Patients must have an immobilization device (e.g. Aquaplast mask) made prior to treatment planning CT scan. Use of a an immobilizing mouthpiece is optional as clinically indicated.

It is preferable to perform treatment planning CT scan with IV contrast if nodal regions or skull base will be targeted and there are no medical contraindications to the use of contrast. The treatment planning CT scan must be performed with the immobilization device and in the treatment position. Slice thickness should be 0.3 cm or thinner.

5.8.2 **Target Delineation**

There should be no Gross Tumor Volume (GTV). The Clinical Target Volume (CTV_60) is defined as the tumor and/or lymph node bed that was dissected. All patients must have a CTV_60. There are two optional CTVs that can be used. Elective areas deemed at risk of subclinical disease that have not been dissected (e.g. elective nodes) can be treated to a lower dose of 54Gy (CTV_54). For areas of highest risk, such as positive margins, or extranodal extension, a high risk CTV (CTV_66) can be used to focally boost these areas in a simultaneous fashion. This treatment volumes should be kept as small as possible.

The Planning Target Volume (PTV_60) should be a 3mm expansion around CTV_60. If additional CTV's are used, they should have their own PTV (e.g. CTV_54 →PTV_54) with a 3mm margin. In general, as the skin is the origin of disease, it will often be targeted. In these cases, the PTV should be allowed to extend outside of the external skin surface and 5mm of custom bolus must be used. When the skin is not part of the target, then the PTV can be shaved out of skin by 3-5mm to enhance planning capabilities.

All plans must be normalized such that 95% of the volume of the PTV_60 is covered with prescription dose of 60 Gy. Additionally: At 1 cc PTV1 volume on the DVH curve, the dose should not be > 110% of the prescribed dose. At a volume of 0.03 cc within the PTV_60 volume on the DVH curve, the dose should not be < 95% of the prescribed dose. For any volume of tissue outside the PTVs that has a size of 1 cc, the dose should not be > 70 Gy.
Elective treatment of lymph nodes is at the discretion of the treating radiation oncologist, and will be determined on a case by case basis. In general, for tumors of the scalp, if lymphatics are targeted, they should include: occipital, parotid, anterior cervical (levels 2-4), and posterior cervical (level 5) nodes. When targeting lymph nodes for tumors of the face (e.g. nose, cheek, temple, eyelid, lip): parotid, anterior cervical (levels 2-4), and submandibular (level 1B) should be included. For ear tumors, pre and post-auricular nodes should be included in addition to parotid, anterior cervical (levels 2-4), and posterior cervical nodes.

For patients with perineural invasion of named nerves, these nerves should be included in the elective CTV_54 to their origin of the skull base. For those with extensive involvement or

proximal involvement adjacent to the skull base, the involved nerves should be targeted bach to the respective nerve ganglion (e.g. Meckel cave for the Gasserion ganglion of the trigeminal nerve).

5.8.3 Critical Normal Structures

The normal tissue volume to be contoured will depend on the site of origin of the cancer. In general, they will include the brainstem, spinal cord, cochlea mandible, glottic larynx, supraglottis, constrictors, esophagus, trachea, oral cavity, lips and parotid and submandibular salivary glands that are not at risk. For tumors of the scalp and other requiring treatment of the skull base, the following should also be included: eyes, lenses, optic nerves, optic chiasm, pituitary, hypothalamus. The PRV (planning risk volume) spinal cord contours will be defined at least 0.5 cm larger in the radial dimension than the spinal cord *(i.e. the cord diameter on any given slice will be 1.0 cm larger than the cord itself*).

5.8.4 Treatment Planning and Delivery

Megavoltage energy photon beam irradiation is required. Static beam intensity modulation or volumetric arc based planning are acceptable for planning.

5.8.5 Image Guidance for IGRT

IGRT with daily conebeam CT is required recommended. If a cone beam CT is not available, portal images should be used. Region-of-Interest (ROI) or “clip box” for fusion should be set to encompass the high dose PTV and adjacent spinal cord. When the skull base is targeted, the globes and optic nerves should routinely be included, if possible, for alignment purposes. Following the registration, the translational and (if the appropriate technology is available) rotational corrections should be applied to the treatment couch. If all the variances are less than 10 mm (this typically corresponds to one half of the usual PRV margin), the treatment can proceed with appropriate corrections; however, re-imaging is not mandatory. If one or more of the corrections are larger than 10 mm, the imaging must be repeated in addition to performing table/positioning adjustments. However, the use of numerous repeat IGRT studies should be avoided (see next section).

5.8.6 Definition of Normal Tissues/Organs at Risk (OARs)

NOTE: Only the parts of the normal tissues/organs at risk outside the PTVs will be considered for dose optimization purposes. Only those OAR that are in proximity to the

treatment volume must be contoured. Contouring OAR that are far from the treated area and will receive negligible doses is unnecessary.

Spinal Cord: The cord begins at the cranial-cervical junction (i.e. the top of the C1 vertebral body). Superior to this is brainstem and inferior to this is cord. The inferior border of the spinal cord is at approximately T3-4 (i.e., just below the lowest slice level that has PTV on it). The spinal cord shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) spinal cord shall be defined. The PRVcord = cord + 5 mm in each dimension. This is irrespective of whether or not IGRT is used.

Brainstem: The inferior most portion of the brainstem is at the cranial-cervical junction where it meets the spinal cord. For the purposes of this study, the superior most portion of the brainstem is approximately at the level of the top of the posterior clinoid. The brainstem shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) brainstem shall be defined. The PRVbrainstem = brainstem + 3 mm in each dimension.

Lips and Oral Cavity: These should be contoured as 2 separate structures as the goal is to keep the lip dose much lower than the oral cavity dose. The definition of lips is self-explanatory. The oral cavity will be defined as a composite structure consisting of the anterior ½ to $^{2}/_{3}$ of the oral tongue/floor of mouth, buccal mucosa, and palate.

OARpharynx/constrictors: This will be defined as the "uninvolved" posterior pharyngeal wall plus adjacent constrictor muscles. This extends from the superior constrictor region (the inferior pterygoid plates level) to the cricopharyngeal inlet (posterior cricoid cartilage level).

Cervical Esophagus: This will be defined as a tubular structure that starts at the bottom of OARpharynx and extends to the thoracic inlet.

Glottic/Supraglottic Larynx (GSL): This will be defined as a "triangular prism shaped" volume that begins just inferior to the hyoid bone and extends to the cricoid cartilage inferiorly and extends from the anterior commissure to include the arytenoids. This includes the infrahyoid but not suprahyoid epiglottis.

Mandible: This includes the entire boney structure of the mandible from TMJ through the symphysis.

Other structures (self explanatory): Optic Nerves, optic chiasm, orbits, lenses, cochlea, lacrimal glands, parotid glands, submandibular glands

Unspecified Tissue Outside the Targets: This will be defined as tissue located between the skull base and thoracic inlet that is not included in either the target volumes or the normal tissues described above.

5.8.7 **Dose Prescription**

Doses to PTVs

See Section 5.8.2 above for definitions of CTVs and PTVs and their prescribed doses. The goal is for 95% of the PTV60 to receive ≥ 2 Gy with a minimum dose (cold spot) of no less than 54 Gy. It is recognized that portions of the PTV60 close to the skin may receive significantly less than 54 Gy if it is not deliberately targeted with custom bolus applied. This is acceptable as long as cold spots within PTV60 do not exist at a depth deeper than 8 mm beneath the skin. For PTV_66, when used, 95% of the volume should get the prescription dose, and <0.03cc should receive >110% of the dose. This criteria does not apply for PTV_54 when used.

Doses to Normal Structures

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

Brainstem: The brainstem should not exceed 56 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). The PRVbrainstem (brainstem +3mm) should be limited to 60Gy. These can be exceeded in cases where the tumor abutted the brainstem and was resected. Max point dose to the brainstem can never exceed 62Gy.

Optic Nerves and Chiasm: These should be limited to a max dose of 54Gy.

Orbits: Should be limited to a max dose of 50Gy with 95% <45Gy. These doses may be exceeded when the tumor is abutting the globe preoperatively and is adjacent to the postoperative bed. The max dose to 0.03cc of the globe can never exceed 52Gy.

Lacrimal Gland: This should be limited to a mean <30Gy whenever possible. This may be exceeded when the tumor location approximated this structure preoperatively and is subsequently at risk or adjacent to the tumor bed.

Lips: Reduce the dose as much as possible. The mean dose should be < 20 Gy when possible.

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

Parotid Glands (not targeted): In most cases, it will be easier to spare one parotid than the other. The treatment planning goal will be for this individual parotid gland to receive a mean dose of <26 Gy.

Submandibular gland (not targeted): If level Ib is not a target, aim to reduce mean contralateral submandibular gland to < 39 Gy.

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

Cervical Esophagus: Reduce the dose as much as possible. Some recommended (but treatment goals include: Mean dose < 30 Gy.

Glottic and Supraglottic larynx (GSL): Reduce the dose as much as possible. The glottic larynx mean dose is recommended to be ≤25 Gy.

Mandible: Reduce the dose as much as possible. Hot spots within the mandible should be avoided. It is recommended that maximum dose within the mandible be < 66 Gy, except in areas overlapping PTV.

Unspecified Tissue Outside the Targets: No more than 1cc of unspecified tissue outside the targets can receive 70 Gy or more

5.8.8 **Radiation Therapy Treatment Interruptions**

Treatment interruptions are strongly discouraged. Treatment breaks must be clearly indicated in the treatment record when they occur. Patients who have treatment interruptions in radiation for >3 weeks will be taken off study. The interruption of radiation therapy for grade 4 mucositis / dermatitis / dysphagia is at the discretion of the treating radiation oncologist. Treatment breaks, if necessary, ideally should not exceed five treatment days at a time and ten treatment days total. Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and not for social or logistical reasons. Pembrolizumab will not be administered during radiotherapy treatment breaks.

5.9 **Subject Withdrawal/Discontinuation Criteria**

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

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression
- Unacceptable adverse experiences as described in Section 7.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements).

5.10 **Clinical Criteria for Early Trial Termination**

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

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

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

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

		Study Treatment (weeks)										**Post-tx**	**Long term f/u**
	Pre-study[a]	1	2	3	4	5	6	7	10	13	16	20[f]	32[f] , 52[f]
Medical History, PE, Vital Signs	x	x	x	x	x	x	x	x	x	x	x	x	x
Height	x												
Weight	x	x	x	x	x	x	x	x	x	x	x	x	x
ECOG PS	x	x	x	x	x	x	x	x	x	x	x	x	x
CBC with Differential	x	x			x			x	x	x	x	x	x
Complete metabolic panel	x	x			x			x	x	x	x	x	x
Concomitant meds	x	x			x			x	x	x	x	x	x
Pregnancy test[b]	x												
TSH	x	x			x			x	x	x	x	x	x
Immune Status History	x												

CT neck and chest (with contrast if possible)[c] (CT Chest preferred, CXR acceptable)	x											x	x
PET/CT and/or MRI[c] (optional)	x												
Dental evaluation[d]	x												
Pembrolizumab		x			x			x	x	x	x		
IMRT			x	x	x	x	x	x					
Adverse event evaluation		x			x			x	x	x	x	x	
Correlatives: submission of tumor tissue[e]	x												
Correlatives: blood[e]	x							x				x	x (52 wks)

a. Pre-treatment evaluations will be performed within 4 weeks prior to registration, unless otherwise specified. This excludes imaging which will be eligible within 12 weeks of registration on study.

b. For women of childbearing potential, pregnancy test must be completed within 2 weeks of beginning treatment.

- c. CT neck and chest CT will be acceptable if done within 12 weeks of trial registration. PET/CT is optional and only recommended if there is concern for gross

residual disease. MRI brain and/or orbits may be important for tumors near the skull base, especially those with perineural invasion. In these cases, MRI is recommended to be obtained at baseline, at wk 20 follow up, and at later follow up visits as clinically indicated. While the routine surveillance images are scheduled for weeks 20, 32 and 52, changes in patient symptoms or persistent symptoms may prompt the clinician to order a CT at any time, as per standard practice.

d. Dental evaluation is recommended for those who will receive significant (>45Gy) dose of radiation to the mandible. However, it is not required.

e. Baseline tumor tissue will be sent to Merck for PD-1 testing. Blood will be collected at designated times (+/- 4 weeks to accommodate patient preference, transportation needs and scheduling needs around coordination of appointments) and sent to the Gastman lab. Additional study of tumor tissue (fresh and/or FFPE) may be done if the patient has consented to other tissue banking protocols.

f. These weeks are suggestions, but are flexible and can be before or after these designated times by 4 weeks to accommodate patient preference, transportation needs and scheduling needs around coordination of appointments.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator. Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Merck for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

The informed consent will a

dhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Medical History

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

7.1.1.4 Prior and Concomitant Medications Review

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

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 Treatment

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

7.1.1.6 Prior Treatment Details

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

7.1.1.7 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.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 11.2). Toxicities will be

characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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

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

7.1.2.2 Physical Exam

The investigators or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening. For all other study visits, including those performed immediately prior to treatment administration, focused physical exams are acceptable.

7.1.2.3 Vital Signs

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

7.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

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

7.1.2.5 Tumor Imaging and Assessment of Disease

As this is an adjuvant trial, there will be no anticipated measureable disease to record. RECIST and other such response criteria do not apply. However, there will be baseline imaging and surveillance imaging to evaluate for locoregional and distant recurrence as specified in the

Trial Flow Chart (section 6.0). In the event of clinical or radiographic recurrence of disease, biopsy to confirm recurrent disease is strongly recommended.

7.1.2.6 Tumor Tissue Collection and Correlative Studies Blood Sampling

Tumor tissue will be sent to Qualtek for PD-1 testing. Blood will be collected on all patients at the times specified in the study flow chart (section 6.1) and sent to the Gastman lab for analysis. Sufficient FFPE may be available from tumor samples to allow for additional correlative study. Also, patients may have fresh tissue available for correlative study if they consented to a separate tissue banking protocol (e.g. IRB 3164 or 15-1580). In these cases, additional experiments may be performed as outlined in section 4.2.3.3. The consent form clearly states that blood will be collected for research purposes and that tumor tissue that is stored in pathology can be used for correlative science.

7.1.3 Laboratory Procedures/Assessments

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

Table 5 Laboratory Tests

Hematology	**Chemistry**	**Other**
Hematocrit	Albumin	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Thyroid stimulating hormone (TSH)
Platelet count	Alanine aminotransferase (ALT)	Blood for correlative studies (recommended)
WBC (total and differential)	Aspartate aminotransferase (AST)	
Absolute Neutrophil Count	Carbon Dioxide ‡	
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*	
Red Blood Cell Count	Calcium	
	Chloride	
	Glucose	
	Potassium	
	Sodium	
	Total Bilirubin	
	Blood Urea Nitrogen	

Laboratory tests for screening or entry into the study should be performed within4 weeks prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.3.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart.

7.1.4.1 Screening

Potentially eligible patients will be screened according to the eligibility checklist. Patients deemed ineligible, as well as those that are offered trial participation and decline enrollment will be recorded as "screen failures."

7.1.4.2 Treatment Period

During the treatment period patients will be seen as follows:

Weeks 1-6: patients will be seen in radiation oncology weekly for their SOC weekly on treatment visit. They will often be assessed in radiation oncology 2-6 weeks post completion of radiotherapy for a routine toxicity check, but this is not mandated.

Weeks 1-16: Patients will be seen by medical oncology every three weeks preceding the administration of Pembroluzimab for toxicity check and lab review. Additional visits may be required during intervening weeks as clinically indicated, but are not mandatory.

7.1.5.3 Follow-Up Visits

A mandatory Safety Follow-Up Visit should be conducted approximately 4 weeks after the last dose of trial treatment. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 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.

Following the initial post treatment follow up visit (week 20), patients will be seen around weeks 32 and 52. These target visit dates are preferred but there will be flexibility in these visits based on provider and patient scheduling and travel needs. Visits performed within 4 weeks before or after these target dates will be acceptable to allow for flexibility in patient transport needs, coordination of appointments and cancellations. At each follow up visit, patients will have vital signs, weight, medical history, focused physical exam, lab evaluation, imaging, ECOG performance status, and correlative blood samples (if applicable), as specified in the Trial Flow Chart (Section 6.0). For patients who experience disease recurrence, they should still be followed for overall survival.

Any patient who fails to make follow up appointments can be contacted by telephone at routinely scheduled follow up times to assess for toxicity, disease and survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.2 **Assessing and Recording Adverse Events**

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

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

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

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

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

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

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

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

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck

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

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

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-

serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

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

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229)

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

7.2.3.1 Serious Adverse Events

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

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

- Is associated with an overdose;
- Is another important medical event
- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.

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

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

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

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

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215-661-6229) at the time of submission to FDA.

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

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and

reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229) Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

7.2.4 **Evaluating Adverse Events**

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

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

Table 6 Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued	

	observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or
	Is a new **cancer;** (that is not a condition of the study) **or**
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units
Action taken	Did the adverse event cause the Merck product to be discontinued?
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing

	the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge.

		(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Merck product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE MERCK PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		

Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck product relationship).**
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.
No, there is not a reasonable possibility Merck product relationship	Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

7.2.5 **Sponsor Responsibility for Reporting Adverse Events**

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

7.2.6 **Investigator Responsibility for Reporting Adverse Events**

It is the Case Comprehensive Cancer Center's Principal Investigator's responsibility to ensure that ALL serious adverse events are reported to the Case Comprehensive Cancer Center's Data Safety Toxicity Committee. This submission is simultaneous with their submission to the Sponsor or other Regulatory body.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Study Design

This is a phase II trial evaluating the addition of concurrent and adjuvant fixed-dose pembrolizumab in combination with standard IMRT, in order to establish safety and estimate efficacy of this regimen to be tested in a subsequent randomized registration trial. At the conclusion of the study, the primary safety endpoint will be proportion of DLT. The primary efficacy endpoint will be 1-year PFS. Progression-free survival (PFS) will be calculated from treatment initiation to disease progression or death from any cause or last follow up.

8.2 Justification of Design and Sample Size:

The target sample size will be 34 patients. Assuming a <10% drop out or ineligibility rate, 37 patients will be enrolled to ensure 34 evaluable patients (all evaluable patients will be analyzed). The sample size was generated based on the primary safety endpoint. DLT $\leq$20% is acceptable and $\geq$40% is unacceptable. If 11 or more of 34 patients experience DLT, this regimen will be considered too toxic. The significance level and power of this design are 6% and 86%, respectively. If 8 or fewer patients experience DLTs, the regimen will be deemed safe to proceed for further study. If 9 or 10 patients experience DLTs, the PI will examine the type, reversibility and duration of DLTs and a careful decision will be made whether to pursue this regimen further in this adjuvant population.

8.3 Statistical Analysis Plan

DLT will be estimated using an exact 95% confidence interval. If 11 or more patients experience DLT the regimen will be considered too toxic. One-year PFS will be estimated using the Kaplan-Meier method and a 95% confidence interval constructed using Greenwood's method. One year PFS outcomes will be assessed overall and also separately for immunocompetent patients vs. immunosuppressed patients (e.g. CLL). These outcomes will be compared to our historical dataset for both subsets respectively. Adverse events will be tabulated by category and grade. The rates of

adverse events will be estimated using an exact 95% confidence. The relationship between 1yr PFS and baseline PD-L1 expression will be assessed using logistic regression. Immunoprofiles in peripheral blood in serial samples will be tested using random effects ANOVA. Bioinformatic analysis will be applied to all genomic and transcriptomic data.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

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

Table 7 Product Descriptions

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

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

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

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to

arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all sub-investigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

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

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures. If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial. The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials. The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents. The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor. Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data,

correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.
The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened. In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct

and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

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

10.5 Quality Management System

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

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate. The investigator will have access to all study related events and outcomes and will have license to analyze and publish this data as he deems fit without any limitations.

The OnCore Database will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for both accrual entry and trial data management. OnCore is a Clinical Trials Management System housed on secure servers maintained at Case Western Reserve University. OnCore properly used is compliant with Title 21 CFR Part 11. Access to data through OnCore is restricted by user accounts and assigned roles. Once logged into the OnCore system with

a user ID and password, OnCore defines roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the OnCore Administrator at oncore-registration@case.edu.

OnCore is designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. This study will utilize electronic Case Report Form completion in the OnCore database. A calendar of events and required forms are available in OnCore.

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI regulations.

Registry Integration

CASE 4311 registry (IRB CC 00192), will share data with IRB 17-069. Data shared will only pertain to mutual patients consented to IRB 17-069 and patients eligible for inclusion in CASE 4311. The clinical data collected by CASE 4311/IRB CC 00192, particularly data regarding cancer recurrence, will be used in conjunction with data collected under IRB 17-069.

10.7 APPENDICES

10.8 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.	

10.9 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)

Appendix 10.10 – Tissue and Blood processing for correlative science

Study #1: Specimen Collection for PD-L1 Expression

- All patients will have slides cut from FFPE tissue blocks for analysis of PD-L1 expression by IHC staining
- FFPE tissue will be obtained from the Tissue Procurement and/or pathology department (CCF) or Biorepository and/or pathology department (UH) and assigned a unique identification number. All other PHI will be redacted from the pathology report.
- Five slides will be cut from each FFPE block for PD-L1 and H&E staining.
  - One slide each for H&E, PD-L1, and Isotype and two for repeat staining if needed
- Results: QualTek Molecular Laboratories Clinical Laboratories will report to Merck and study investigators.
- Residual Material: FFPE specimens will be retained by Cleveland Clinic and University Hospitals in anatomic pathology per their routine, and made available for future use as indicated.

Study #1 Specimens shipped to:

QualTekMolecularLaboratories
MISP Receiving
300 Pheasant Run
Newtown, PA USA 18940
Phone: 215-504-7402
Fax: 805-830-6379
MISPsamples@qmlabs.com

Specimen Type	Collection Time Points	Collection Information and Requirements	Shipping
Five slides from primary tumor FFPE blocks	Baseline Tumor specimen	Sections will be 4 micron thickness onto Fisher ProbeOn Plus Slides, Cat Number 22-230-900. Tissue sections must be placed on the painted/ textured side of the slide.	Slides shipped cold (2-8ºC) and in the dark using QualTek-supplied packing materials.

Study #2: Blood Collection for Immune Biomarker Analysis

- All patients will have blood collected at specific time points (pre-treatment and weeks 7, 20, and 52). +/- 4 weeks is allowed on follow up visits.
- At each time point, up to 50cc of blood will be collected and processed by research laboratory personnel (Dr. Gastman, PI) to isolate lymphocytes and freeze for further analysis.
- Specimens will be assigned the same unique identification number used for Study #1 and any other personal health information (PHI) will be redacted from the pathology report.
- Results: Research laboratory personnel will report to Merck and study investigators.
- Residual Material: cryopreserved specimens will be retained by the research laboratory until the study conclusion.

For CC: Samples will typically be collected by CRA. Gastman lab will then be contacted as follows:

Please call Ye Tian (Field) (Gastman Lab) at 773-226-2782 for pickup. If there is no response, please page Dr. Brian Gastman at 216-401-4776. The samples will be picked up by Gastman lab personnel and transported to:

9500 Euclid Avenue
Gastman Laboratory
Lerner Research institute, NE4-217
Cleveland, Ohio 44195
Phone: (216) 444-0202

For UH: Samples will be collected by research nurse. These samples should be collected by the research nurse ***before 12PM***, to allow sufficient time for the TRPC (translational research and pharmacology core) to courier the samples to CC before 5pm. Generally, samples cannot be received at CC after 5PM. In the event that samples are late, they should still be sent to CC.

The research nurse will then contact the Translational Research and Pharmacology Core of UH (Attn: Erin Hohler) at 216-286-3889 or 216-286-3890, pager 33471, emh14@case.edu. The tissue will then be picked up by the TRPC staff and they will arrange for courier of the tissue to Cleveland Clinic.

The TRPC should then courier the blood same day to:

Cleveland Clinic Central Biorepository
Pathology and Lab Medicine Institute- L15
Surgical Pathology- Tissue Procurement
2119 East 93rd St
Cleveland, Ohio 44106
Phone (216)444-0047

When specimens arrive at L15, please call Ye Tian (Fields) (Gastman Lab) at 773-226-2782 for pickup. If there is no response, please page Dr. Brian Gastman at 216-401-4776. Also, please email the following personnel notifying them that a sample was collected: samsaj@ccf.org; robinss@ccf.org; koyfmas@ccf.org;tisscenterap@ccf.org;THOMPSS9@ccf.org; tainy2@ccf.org gastmab@ccf.org

Specimen Type	Collection Time Points	Collection Information and Requirements	Shipping
Up to 50cc of peripheral whole blood in heparin (green top) or EDTA (lavender/purple top) tubes	Pre-treatment, weeks 7, 20, and 52	Lymphocytes isolated by centrifugation over Ficoll gradient and stored frozen in FBS/10% DMSO in 1.8 mL cryovials. Samples should be stored at -80ºC	CCF: After collection, blood tubes will be delivered to Gastman Lab. UH: After collection, blood tubes will be sent to anatomic pathology via courier (L-15).

Study #3 and #4: Fresh or FFPE Tissue for Immune Biomarker Analysis and Tumor Gene Expression Analysis (Optional)

- For patients who consent to other IRB-approved tissue banking protocols:
  - Fresh tumor tissue will have been received, de-identified, processed and stored (frozen). RNA isolation may have also taken place for gene expression analysis
  - This tissue may be sent to the Gastman lab for experimentation.
- FFPE tissue may be obtained in patients for whom fresh tissue is not available:
  - FFPE tissue will be obtained from the Tissue Procurement (CC) or Biorepository (UH) tissue bank and assigned a unique identification number. All other PHI will be redacted from the pathology report.
  - Up to 10 slides will be cut from each tissue block for immune biomarker staining
  - A small punch will be taken for RNA isolation for subsequent gene expression analysis
- Results: Research laboratory personnel will report to Merck and study investigators.
- Residual Material: cryopreserved specimens, tissue slides, and genetic material will be retained by the research laboratory until the study conclusion.

Specimens shipped to:

For **Cleveland Clinic:**
Gastman Laboratory
Lerner Research Institute
NE4-217
Phone: 216-444-0202

For **University Hospitals:**

Cleveland Clinic Central Biorepository
Pathology and Lab Medicine Institute- L15
Surgical Pathology- Tissue Procurement
2119 East 93rd St
Cleveland, Ohio 44106
Phone (216)444-0047

When specimens arrive at L15, please call Ye Tian (Field) (Gastman Lab) at 773-226-2782 for pickup. If there is no response, please page Dr. Brian Gastman at 216-401-4776.
Also, please email the following personnel notifying them that a sample was collected: samsaj@ccf.org; robinss@ccf.org; koyfmas@ccf.org; tisscenterap@ccf.org; THOMPSS9@ccf.org; tiany2@ccf.org gastmab@ccf.org

Specimen Type	Collection Time Points	Collection Information and Requirements	Shipping
Fresh primary tumor tissue or up to 10 slides cut from FFPE tissue blocks and 3mm punches taken from FFPE tumor blocks.	Time of primary surgical resection or from baseline tumor specimen	Tumors dissociated by enzymatic digestion followed by freezing in FBS/10% DMSO for subsequent analysis. Samples should be stored at -80°C. RNA isolation from fresh tissue or FFPE punches by organic extraction/ silica column purification.	Tumor tissue will be delivered to Gastman lab.

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12.0
SUMMARY OF CHANGES v08/03/2017

Protocol Date	Section	Change
08/03/17	2.1	Safety run in period and Phase II portion was deleted from this section
08/03/17	4.2.2	The following was added to this section: A pilot study that investigated the safety of adding Pembrolizumab to head and neck IMRT in addition to weekly cisplatin was recently presented at ASCO 2017. Powell, et al reported excellent safety profile of 27 patients with locally advanced head and neck cancer treated with chemoradiation with weekly cisplatin, and 70Gy in 35 fractions of IMRT along ith Pembrolizumab 200mg fixed dose IV every 3 weeks beginning 4-7 days prior to the initiation of radiation 2 doses concomitant with IMRT and 5 additional doses post IMRT. 21 patients (78%) completed all planned doses of Pembrolizumab. 3 discontinued due to irAEs (G2 peripheral motor neuropathy, G3 AST elevation, G1 Lhermitte-like syndrome). 3 discontinued due to protocol reasons (early neck dissection -2 pts, prolonged hospitalization-1 pt). All pts completed the full radiation dose (70 Gy) without significant delay (defined as > 5 days). 23 (85%) received the goal target dose of cisplatin (≥200 mg/m2). There was one patient death due to concurrent illness, unrelated to treatment.[18] Based on these results, the NRG Oncology HN-003 study which was designed as a phase I safety study of the addition of Pembrolizumab to postoperative head and neck IMRT and weekly cisplatin discontinued their planned phase I safety study and converted to an open label efficacy signal study. We therefore feel quite confident in the safety of our proposed regimen as our study involves less extensive IMRT fields and does not include any concurrent chemotherapy. We will however monitor DLTs very carefully and include that as a co-primary endpoint of the study.
08/03/17	4.2.3.2	Initial safety run in information deleted from this section
08/03/17	5.1.1	4) Lymphoid malignancies deleted. Patients with a history of chronic lymphoid or leukemic malignancies which are not under active therapy (no active therapy within the last 3 months) will be eligible.
08/03/17	5.1.2	4) Lymphoid malignancies deleted Patients with chronic lymphoid/leukemic malignancies that have undergone treatment in the last 3 months will be ineligible.
08/03/17	5.4	Safety run in period and Phase II portion was deleted from this section
08/03/17	8.0	Initial safety run in period deleted from this section

Protocol Date	Section	Change
08/03/17	8.3	One year PFS outcomes will be assessed overall and also separately for immunocompetent patients vs. immunosuppressed patients (e.g. CLL). These outcomes will be compared to our historical dataset for both subsets respectively. Added to this section
08/03/17	Table 1	Removed coagulation section
08/03/17	7.1.5.3	Changed 2nd paragraph "visits performed within 3 weeks…" to within 4 weeks…
08/03/17	Appendix 10.10	Study #2, 3 and 4 lab address change for Cleveland Clinic from NE6-251 to NE4-217
		Protocol date change to 08/03/2017 on page 1 and the footer

SUMMARY OF CHANGES v08/29/2017

Protocol Date	Section	Change
08/29/17	5.0 #7	Patients with chronic lymphoid or leukemic malignancies are eligible with or without active disease as long as they have not had treatment within the past three months Added to this section
08/29/17		Protocol date change to 08/29/2017 on page 1 and the footer

SUMMARY OF CHANGES v09/27/2017

Protocol Date	Section	Change
09/27/17	5.1.1#4	Patients with chronic lymphoid or leukemic malignancies are eligible with or without active disease as long as they have not had treatment within the past three months Added to this section
09/27/17	5.1.2 #7	Patients with chronic lymphoid or leukemic malignancies are eligible with or without active disease as long as they have not had treatment within the past three months Added to this section
09/27/17		Protocol date change to 09/27/2017 on page 1 and the footer

SUMMARY OF CHANGES v08/30/2018

Protocol Date	Section	Change
08/30/18	7.1.2.6 page 49	Removed Laboratory tests for screening or entry into the study should be performed within 10 days prior to the first dose of treatment. Added Laboratory tests for screening or entry into the study should be performed within 4 weeks prior to the first dose of treatment.
08/30/18	Study #2 page 71	Removed lab contact information for Lukas Pfannenstiel 443-622-9736. Added contact information for Ye Tian (Field) 773-226-2782. konczov@ccf.org was removed and tiany2@ccf.org was added.
08/30/18	Study #3 & 4 page 73	Removed lab contact information for Lukas Pfannenstiel 443-622-9736. Added contact information for Ye Tian (Field) 773-226-2782. konczov@ccf.org was removed and tiany2@ccf.org was added.
08/30/18	7.2.1	Changed fax # to 215-661-6229
08/30/18	7.2.2	Changed fax # to 215-661-6229
08/30/18	7.2.3.1	Added a note further clarifying serious adverse events, Changed fax # to 215-661-6229
08/30/18	7.2.3.2	Changed fax # to 215-661-6229, Removed, “this trial site guidance for assessment and follow-up of these criteria can be found in the investigator trial file binder (or equivalent) Removed additional adverse events

SUMMARY OF CHANGES v10/30/2018

Protocol Date	Section	Change
10/30/2018	5.1.1	Added: Invasion of the axial skeleton or skull base or skull base foramina and Tumor greater that 2cm with any 1 additional feature Removed: Note: Not all patients with T2N0 cancer with one additional risk factor may be ideal candidates for this study, such as patients with only focal perineural invasion without other adverse features. Clinical judgment should be used by recurrence with radiation alone.
10/30/2018	6.0	Added: (CT chest preferred, CXR acceptable) and superscript c: CT neck and chest CT will be acceptable if done within 12 weeks of trial registration. PET/CT is optional and only recommended if there is concern for gross residual disease. MRI brain and/or orbits may be important for tumors near the skull base, especially those with perineural invasion. In these cases, MRI is recommended to be obtained at baseline, at wk 20 follow up, and at later follow up visits as clinically indicated. While the routine surveillance images are scheduled for weeks 20, 32 and 52, changes in patient symptoms or persistent symptoms may prompt the clinician to order a CT at any time, as per standard practice. Removed: CT neck and chest will be acceptable if done within 12 weeks of trial registration. PET/CT is optional and only recommended if there is concern for gross residual disease. MRI brain and/or orbits may be important for tumors near the skull base, especially those with perineural invasion. In these cases, MRI is recommended to be obtained at baseline, at wk 20 follow up, and at later follow up visits as clinically indicated. While the routine surveillance CT are scheduled for weeks 20, 32 and 52, changes in patient symptoms or persistent symptoms may prompt the clinician to order a CT at any time, as per standard practice guidelines.
10/30/2018		Protocol date change to 10/30/2018 on page 1 and the footer

SUMMARY OF CHANGES v12/04/2019

Protocol Date	Section	Change
12/04/19	Page 1	Updated protocol date to 12/04/2019 and footer protocol date to 12/04/2019.
12/04/19	Page 67	Added registry integration information.