Immunotherapy with MK-3475 in locoregionally advanced, surgically resectable head and neck squamous cell carcinoma

Washington University School of Medicine
Department of Otolaryngology
660 South Euclid Avenue, Campus Box 8115
St. Louis, MO 63110

Protocol #: 201412118
Version Date: 10/28/2024

Coordinating Center: Washington University School of Medicine

Principal Investigator: Douglas R. Adkins, M.D.
Phone: (314) 362-4471
E-mail: dadkins@wustl.edu

Sub-Investigators	Institution	Modality
Ravindra Uppaluri, M.D., Ph.D.	Dana Farber Cancer Institute	Otolaryngology
Max Artyomov, Ph.D.	Washington University	Pathology/Immunology
Rebecca Chernock, M.D.	Washington University	Head & Neck Pathology
Hiram Gay, M.D.	Washington University	Radiation Oncology
Nsangou Ghogomu, M.D.	Washington University	Otolaryngology
Dorina Kallogjeri, M.D., MPH	Washington University	Biostatistics
Brian Nussenbaum, M.D.	Washington University	Otolaryngology
Randal Paniello, M.D.	Washington University	Otolaryngology
Jay Piccirillo, M.D.	Washington University	Otolaryngology/Biostatistics
Jason Rich, M.D.	Washington University	Otolaryngology
Robert D. Schreiber, Ph.D.	Washington University	Pathology/Immunology
Wade Thorstad, M.D.	Washington University	Radiation Oncology
Tanya M. Wildes, M.D.	Washington University	Medical Oncology
Gavin P. Dunn, M.D., Ph.D.	Washington University	Neurosurgery

Study Drug: MK-3475 (pembrolizumab, Keytruda)

IND #: 124877
Clinical Trials.gov #: NCT02296684

Immunotherapy with MK-3475 in locoregionally advanced, surgically resectable HPV-negative head and neck squamous cell carcinoma

Protocol Revision History

Initial Approval Version	**12/12/2014**
Amendment #1 Version	**02/06/2015**
Amendment #2 Version	**08/07/2015**
Amendment #3 Version	**04/26/2016**
Amendment #4 Version – PRMC only	**09/09/2016**
Amendment #4 Version	**09/30/2016**
Amendment #5 Version	**12/29/2016**
Amendment #6 Version	**12/11/2017**
Amendment #7 Version	**10/28/2024**

Immunotherapy with MK-3475 in locoregionally advanced, surgically resectable HPV-negative head and neck squamous cell carcinoma

Principal Investigator Signature Page

Principal Investigator (printed):

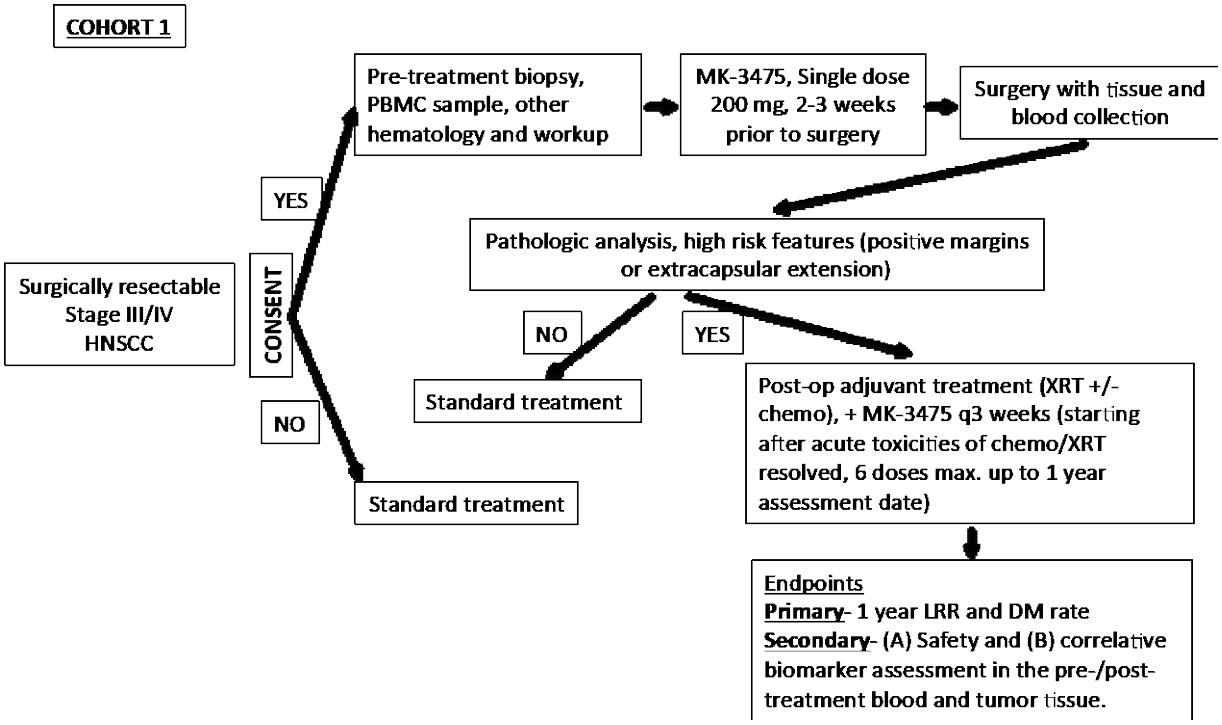
Name of Institution:

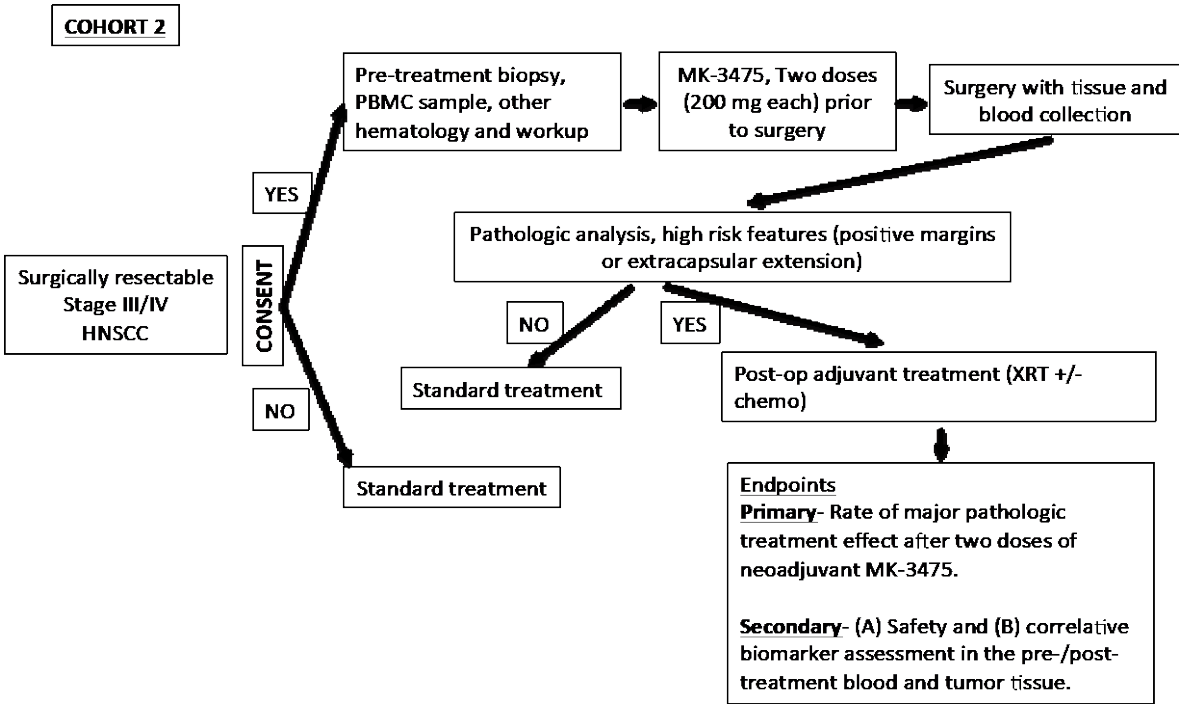
PI Signature *Date*

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/HRPO procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

Immunotherapy with MK-3475 in locoregionally advanced, surgically resectable HPV-negative head and neck squamous cell carcinoma

SCHEMA





Glossary of Abbreviations

AE/irAE	Adverse event/immune-related adverse event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
CBC	Complete blood count
CMP	Complete metabolic panel
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DM	Distant metastases
DNA	deoxyribonucleic acid
DSM	Data and Safety Monitoring
ECI/irECI	Event of clinical interest/immune-related event of clinical interest
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
HIV	Human Immunodeficiency Virus
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papilloma virus
HRPO	Human Research Protection Office (IRB)
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IULN	Institutional upper limit of normal
LRR	Locoregional recurrence
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
OHRP	Office of Human Research Protections
OPSCC	Oropharyngeal squamous cell carcinoma
PBMC	Peripheral blood mononuclear cell
PI	Principal investigator
PT	Prothrombin time
PTT/aPTT	Partial thromboplastin time
QASMC	Quality Assurance and Safety Monitoring Committee
RECIST	Response Evaluation Criteria in Solid Tumors (Committee)
RNA	Ribonucleic acid
SAE	Serious adverse event
SCC	Siteman Cancer Center
SUSAR	Suspected unexpected serious adverse reaction
UPN	Unique patient number

Table of Contents

1.0 BACKGROUND AND RATIONALE

1.1 HPV-negative Head and Neck Squamous Cell Carcinoma

Current therapies for the treatment of stage III/IV locally advanced human papillomavirus (HPV)-negative head and neck squamous cell carcinomas (HNSCC) result in cure in 40-50% of patients, with many of the remaining suffering from locoregional recurrences (LRR) and distant metastases (DM) resulting in patient demise. Although the last decade has seen a near epidemic growth of HPV-induced oropharyngeal squamous cell carcinomas (OPSCC), the "classical" carcinogen-induced HNSCCs still represent the major subtype that causes the greatest patient mortality. Whereas current treatment of HPV-induced OPSCC results in 80-90% cure rates, multimodality approaches in non-HPV-related HNSCC are not nearly as successful. Thus, there is a pressing need for development of novel therapeutics in carcinogen-induced HNSCC.

Standard of care treatment for loco-regionally advanced disease includes definitive combined chemotherapy and radiation or surgical extirpation followed by adjuvant radiation without or with chemotherapy. In the latter approach, post-operative adjuvant treatment is dictated by pathologic findings where patients either receive radiation alone or more intensive combined chemotherapy and radiation. Despite the addition of these modalities, these "high risk" radiation- and chemotherapy-treated subgroup of patients (those with positive margins or lymph node extracapsular extension) suffer disease-specific mortality and could most benefit from novel therapeutic intensification approaches such as adjuvant immunotherapy. This fact is illustrated in clinical trials that first demonstrated superiority of combined postoperative chemoradiation regimens where LRR/DM was still observed in 35% of patients within 2 years after surgery and chemoradiation (1, 2).

1.2 MK-3475

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades (3). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies (4-8) . 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) (9, 10). The structure of murine PD-1 has been resolved (11). PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic

tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade (10, 12-14). 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 (6, 15). 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 (16, 17). Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells (18). 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 (3-7). 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 (17). 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) (19) . 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.

MK-3475 (previously known as SCH 900475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

Please refer to the IB for preclinical and clinical data.

1.2.1 Rationale for Dosing

The dose regimen of 200 mg Q3W of pembrolizumab is planned for all urothelial cancer trials. Available PK results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at a given dose among tumor types. An open-label Phase 1 trial (PN001) in melanoma subjects is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No maximum tolerated dose (MTD) has been identified.

In KEYNOTE-001, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive pembrolizumab at 2 mg/kg versus 10 mg/kg Q3W. The overall response rate

(ORR) was 26% (21/81) in the 2mg/kg group and 26% (25/79) in the 10 mg/kg group (full analysis set (FAS)). The proportion of subjects with drug-related adverse events (AEs), grade 3-5 drug-related AEs, serious drug-related AEs, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group.

Available pharmacokinetic results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at a given dose among tumor types. Population PK analysis has been performed and has confirmed the expectation that intrinsic factors do not affect exposure to pembrolizumab to a clinically meaningful extent. Taken together, these data support the use of lower doses (with similar exposure to 2 mg/kg Q3W) in all solid tumor indications. 2 mg/kg Q3W is being evaluated in NSCLC in PN001, Cohort F30 and PN010, and 200 mg Q3W is being evaluated in head and neck cancer in PN012, which are expected to provide additional data supporting the dose selection.

Selection of 200 mg as the appropriate dose for a switch to fixed dosing is based on simulation results indicating that 200 mg will provide exposures that are reasonably consistent with those obtained with 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed using available data from 476 subjects from PN001. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose, with some tendency for individual values to range slightly higher with the 200 mg fixed dose. The slight increase in PK variability predicted for the fixed dose relative to weight-based dosing is not expected to be clinically important given that the range of individual exposures is well contained within the range of exposures shown in the melanoma studies of 2 and 10 mg/kg to provide similar efficacy and safety. 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 tumor types and indication settings.

1.3 Study Rationale

From a therapeutic standpoint, HNSCC genomics-driven oncologic approaches have identified potential targets but may be limited by inter- and intratumoral heterogeneity. With this background, HNSCC has several features that make it ideal for checkpoint blockade-based immunotherapeutic approaches. First, supporting a role for immune surveillance, epidemiologic evidence suggests that immunodeficient states increase HNSCC (reviewed in (20)). Second, although there is some mixed data, analysis of immune infiltrates suggests that an ongoing immune response occurs in HNSCC patients. Finally, as a carcinogen-related malignancy, the genomic landscape of these cancers bears a rich repertoire of mutations that represent an array of antigenic targets for immune-based therapeutics. These three points parallel features of patients with NSCLC where MK-3475 has successfully achieved clinically meaningful responses and thus serves as a critical rationale for a similar approach in HNSCC.

In support of this approach, data presented at ASCO 2014 in HNSCC patients with recurrent metastatic disease showed encouraging results with 20% of patients achieving best overall

response (Seiwert et al, ASCO 2014, Abstract 6011). In this study, 78% of patients were classified as PD-L1 positive (>= 1% of tumor cells staining for PD-L1) and there was a trend towards better response in the PD-L1 positive patients. Data from other studies shows that expression of PD-L1 on HNSCC tissues varies between 46-100% (reviewed in (21)). The variability in expression is likely due to a combination of factors including the specific antibody used for staining and head and neck subsite. In summary, there is a strong foundation for MK-3475 immunotherapy based treatment intensification in patients with locally advanced HNSCC.

1.3.1 Rationale for MK-3475-based treatment intensification in the neoadjuvant and post-operative setting

The key problem in the management of locally advanced HNSCC is the 35% LRR/DM rate despite aggressive surgical and post-operative chemoradiation regimens. Importantly, the rationale for combined chemoradiation in the post-operative setting is that cisplatin-based therapy acts as a radiosensitizer. Previous intensification studies with additional chemotherapy have not shown a survival benefit in this group of patients, and these studies have been complicated by toxicity and patient compliance issues. Thus, no other adjuvant therapies have been identified to reduce the 35% LRR/DM rate.

MK-3475 immunotherapy as an intensification approach is well justified in the high-risk HNSCC population because (1) PD-L1 expression is common in HNSCC, (2) MK-3475 displays activity in the recurrent/metastatic setting, and (3) immunotherapy may be ideally suited for the minimal residual disease post-operative setting. Our novel trial design aims to define whether MK-3475 immunotherapy can improve outcomes in the initial treatment of advanced stage HNSCC patients using a combined neoadjuvant with post-operative adjuvant approach. The neoadjuvant portion will allow us to analyze patient tissue pre- and post-treatment. Here, the patient serves as their own control, which allows for important treatment effect comparisons. Importantly, although speculative, this pre-operative dose coupled with surgery may enhance tumor specific immune responses. Surgical extirpation likely releases significant tumor antigens and stimulates wound healing inflammation that combined with checkpoint blockade may prime antigen specific T cell responses. At present, it is unclear which advanced stage patients benefit from combined treatment but clearly 35% of them fail this therapy. Thus, MK-3475 will be continued in this high-risk group after completion of and recovery from chemoradiation. Although we considered combining MK-3475 with the post-operative chemoradiation, concerns about toxicity that will alter standard of care treatments precluded this option. In addition, there is no data on the combination of MK-3475, cisplatin, and radiation treatment. In summary, there is a strong foundation for MK-3475 immunotherapy based treatment intensification in patients with locally advanced HNSCC.

1.4 Correlative Studies Background

The goal of the correlative work will be to determine if there is any correlation between the primary endpoint and biomarkers within peripheral blood or in the tumor specimens. The key advantage of this study is the availability of not only matched pre- and post-treatment peripheral blood but also pre- and post-treatment tumor tissue from treatment naïve patients. Existing data suggest that tumor expression of PD-L1 correlates with patient responses. However, the understanding of predictive biomarkers is incomplete. Thus, we propose to not only incorporate

PD-L1 tumor staining on the neoadjuvant biopsies of pre- and post-treatment tumors, but to also analyze molecular signatures in peripheral blood and tumor tissues. Together, these data will lead to an improved understanding of those patients who may benefit most from MK-3475 therapy.

We hypothesize that MK-3475 will result in increased T cell responses in peripheral blood as detected by multiparameter analysis and will define a unique biomarker molecular signature of MK-3475 activity and (2) MK-3475 treatment will reveal an intratumoral signature of an immune response to HNSCC. The goal will be to determine if there is any correlation between the primary endpoint and biomarkers within peripheral blood or in the tumor specimens. The key advantage of this study is the availability of not only matched pre- and post-treatment peripheral blood but also pre- and post-treatment tumor tissue from treatment naïve patients. In addition to standard IHC methodology, we will aim to generate biomarkers that will be linked to patient outcomes identified in the primary endpoint. We will apply a novel machine learning algorithm to histopathologic slides to identify predictive biomarkers of treatment response using computational analysis of the spatial organization of tumor infiltrating lymphocytes in relation to tumor cells. Using our immunomonitoring core, we will apply CyTOF or FACS based multiparameter analysis of PBMCs pre- and post- MK-3475 treatment to delineate immune cell subsets and cell surface activation markers. If sufficient pre-treatment tumor tissue is available, FACS or CyTOF will also be applied to tumor infiltrating immune cells. We will deconvolute RNA-Seq data from pre- and post-treatment blood and tumor tissue to identify not only immune cell populations but also markers of immune cell activation. Finally, conventional genomics-based analysis of the tumor cells themselves may provide insight into intrinsic mediators of responsiveness or resistance.

1.5 Rationale for Retrospective Review of OCSCC Surgical Data

An early unexpected observation noted after treating 18 patients on this prospective trial (as of September 2016) is the very low rate of patients with high-risk pathologic features after one dose of MK-3475 followed by surgery. The impact of this observation is that the fraction of patients undergoing surgery on this study who prove to have high risk pathologic features is much lower than expected, meaning that a lower number of patients than expected go on to receive adjuvant chemotherapy or chemoradiation followed by adjuvant MK-3475. We expected that 85% of patients on this trial would have these high-risk features. The reason for this observation is unclear but could include stage decrease due to the neoadjuvant MK-3475, or it could be that our original assumption that 85% of patient would have high risk features was too high. Therefore, we are amending this protocol to include a retrospective review of Washington University's experience with patients with clinically locally advanced oral cavity SCCs who undergo surgery to determine the historical percentage of these patients that have high risk pathologic features and then compare these data to this endpoint in this prospective trial. Please refer to Section 16.0 for a description of this embedded retrospective review.

1.6 Rationale for Interim Analysis of All Pembrolizumab-Treated Patients

As described in Section 1.5, we have observed a low rate of patients with high-risk pathologic features with neoadjuvant pembrolizumab treatment. These findings are unexpected and may have significant impact for clinical outcomes in these patients. Given these findings, we are amending this protocol to perform an interim analysis of all 20 patients enrolled so far with the intent to present this data at upcoming scientific meetings. We will review clinical and pathologic staging, rates of locoregional recurrence and distant metastasis since neoadjuvant pembrolizumab

treatment and correlative data that are available to date. The latter include genomic information completed on a subset of the 20 patients, PD-L1 staining and serum cytokine responses.

1.7 Rationale for Performing CT Scan after Neoadjuvant Dose Prior to Surgery

We are amending this protocol to include a study CT scan of the head and neck with contrast to assess whether RECIST criteria can be used to identify responder patients after the neoadjuvant dose. As described above several responses have been observed with the neoadjuvant dose. However, definition of "response" is based on a combination of observed tumor specific clinical changes, patient subjective reports and evaluation of pathology specimens after definitive surgical resection. To better define objective responses, we will also perform a dedicated head and neck study CT scan in the pre-surgery period to compare to the baseline, standard of care CT.

1.8 Rationale for Addition of Cohort 2

Patients enrolled to cohort 2 will be treated with two (vs. one) neoadjuvant doses of MK-3475, but will not receive adjuvant MK-3475.

The interim analysis of the first 25 patients (Section 1.6) showed the following observations:

1. No serious drug-related AEs or unexpected surgical delays/complications.
2. No LRR/DM events in the first 14 patients with > 1 year of follow-up.
3. Rate of high risk pathologic features 42%, much lower than the expected rate of 85% and the historical institutional rate of 71%.
4. Pathologic evidence of treatment effect was noted in 42% of patients. Twenty-five percent of patients had tumor samples with a major ($\geq$ 50%) treatment effect. Treatment effect was defined as tumor necrosis and/or giant cell/histiocytic reaction to keratinous debris distinct from growing tumor and only seen with therapy.
5. Patient 15 underwent staged neck dissections. The first neck dissection (right side) showed no treatment effect. The second neck dissection (left side) showed extensive treatment effect. In this case, the additional time between the neoadjuvant dose of MK-3475 and the second surgery is one possible explanation for the presence of treatment effect in the tissue removed at the second surgery but lack of treatment effect in the tissue removed at the first surgery. This case suggests that additional time between administration of neoadjuvant MK-3475 and surgery is needed to fully deploy the immunologic therapeutic effect of MK-3475.

Clinical-to-pathologic tumor down-staging, pathologic treatment effect, and lack of LRR/DM events in the first 14 patients with one year of follow-up are impressive evidence of the anti-tumor activity of MK-3475. Down-staging and treatment effect can only be related to the neoadjuvant pembrolizumab, and since most patients did not have high risk features and thus did not receive adjuvant MK-3475. The lack of relapse events to date may be primarily due to the single dose of neoadjuvant MK-3475.

The original hypothesis of the protocol was that adjuvant MK-3475 would reduce the LRR/DM rate in patients with high risk pathology features; however, the unexpectedly low rate of patients with high risk pathology features and thus low number of patients given adjuvant MK-3475 coupled with the absence of LRR/DM events to date make it impossible to prove the original hypothesis in such a small study.

Beginning with Amendment #6, we plan to focus on pathologic treatment effect as an important endpoint. In other cancers, this endpoint has proven to be an excellent early surrogate of later relapse events. Steps taken to increase pathologic treatment effect correlated with lower relapse events in osteosarcoma, and breast and anorectal cancers. The primary objectives for Cohort 1 (one dose of neoadjuvant MK-3475) and Cohort 2 (two doses of neoadjuvant MK-3475) will be to determine the major pathologic treatment effect. To collect additional data on this endpoint for one dose of neoadjuvant MK-3475, accrual to Cohort 1 will continue until Cohort 2 opens.

Cohort 2 will be treated with two doses of neoadjuvant MK-3475: dose 2 given 21 days (+/- 3) after dose 1 and 14-24 days before surgery. We hypothesize that two doses of neoadjuvant MK-3475 will result in a major pathologic treatment effect in 50% of patients compared to the rate of 25% seen in Cohort 1 treated with one neoadjuvant dose of MK-3475. We estimate that a sample size of 26 patients in Cohort 2 is needed to allow us to detect with 80% power at the one sided alpha level of 0.05 a major pathologic treatment rate of 50%, as a significant improvement over the 25% rate in the single dose use cohort. Considering a 15% drop out rate, we plan to enroll 31 patients in Cohort 2.

2.0 OBJECTIVES

2.1 Primary Objectives

1. Cohorts 1 and 2: To determine the locoregional recurrence rates in patients with stage III/IV HNSCC being treated with surgical therapy followed by indicated adjuvant therapy intensified by MK3475.

2. Cohorts 1 and 2: To determine the distant failure rate in patients with stage III/IV HNSCC being treated with surgical therapy followed by indicated adjuvant therapy intensified by MK-3475

3. Cohort 1 only: To determine the rate of major pathologic treatment effect after one dose of neoadjuvant MK-3475.

4. Cohort 2 only: To determine the rate of major pathologic treatment effect after two doses of neoadjuvant MK-3475.

2.2 Secondary Objectives

1. Cohorts 1 and 2: To evaluate the safety of treatment with MK-3475 as measured by occurrence of adverse events.

2. Cohorts 1 and 2: To evaluate the safety of treatment with MK-3475 as measured by surgical complications or delays.

3. Cohorts 1 and 2: To determine the LRR/DM rates.

4. Cohorts 1 and 2: To evaluate overall survival and event-free survival rates. Overall survival will be defined as time from surgery to death from any cause. Event free survival will be defined as time from surgery to time to disease recurrence, distant metastasis, new primary, or death due to any cause, whichever occurred first.

5. Cohorts 1 and 2: To evaluate overall survival and event-free survival rates differences by presence versus absence of recurrent genomic alterations.

2.3 Exploratory Objective

To compare the anti-HNSCC immune response before and after MK-3475 including assessment of PD-L1 expression, immune function, and molecular signatures of activation in the pre- and post-treatment blood and tumor tissue.

To apply a machine learning algorithm to hematoxylin and eosin-stained slides of tumor from baseline and surgically-resected specimens to characterize the spatial organization of tumor-infiltrating lymphocytes and identify spatial architectures associated with treatment response and survival outcomes.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Histologically or cytologically confirmed stage III or IV HNSCC oral cavity, hypopharynx, oropharynx, larynx (excluding p16 or HPV-positive oropharynx primaries and sinonasal primaries).

2. Measurable disease defined as lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with CT scan, as ≥20 mm by chest x-ray, or ≥10 mm with calipers by clinical exam by RECIST 1.1.

3. At least 18 years of age.

4. ECOG performance status ≤ 1 (see Appendix A).

5. Normal bone marrow and organ function as defined below:
   a. Absolute neutrophil count ≥ 1,500/mcl
   b. Platelets ≥ 100,000/mcl
   c. Hemoglobin ≥ 9 g/dL
   d. Total bilirubin ≤ 1.5 x IULN OR direct bilirubin ≤ IULN for patients with total bilirubin > 1.5 x IULN
   e. AST(SGOT)/ALT(SGPT) ≤ 2.5 x IULN (or ≤ 5 x IULN for patients with liver metastases)
   f. Serum creatinine ≤ 1.5 x IULN OR creatinine clearance by Cockcroft-Gault ≥ 30 mL/min/1.73 m^2 for patients with creatinine levels > 1.5 x IULN
   g. INR ≤ 1.5 x IULN unless patient is receiving anticoagulant therapy as long as INR or PTT is within therapeutic range of intended use of anticoagulants

h. aPTT ≤ 1.5 x IULN unless patient is receiving anticoagulant therapy as long as INR or PTT is within therapeutic range of intended use of anticoagulants

6. Sexually active women of childbearing potential and men must agree to use 2 methods of contraception (hormonal or barrier method of birth control, abstinence) prior to study entry, for the duration of study participation, and for 120 days after last dose of MK-3475. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

7. Ability to understand and willingness to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

3.2 Exclusion Criteria

1. Prior treatment for head and neck cancer.

2. Patients with HPV-positive or p16-positive oropharyngeal SCCA.

3. Patients with sinonasal SCCAs

4. Patients with metastatic SCCA neck disease with an unknown primary tumor site

5. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

6. Received a live vaccine within 30 days prior to the first dose of MK-3475. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. FluMist) are live attenuated viruses and are not allowed.

7. A history of other malignancy ≤ 3 years previous with the exception of previous head and neck cancer treated only by surgery, basal cell or squamous cell carcinoma of the skin which were treated with local resection only, or carcinoma *in situ* of the cervix.

   Note: patients with synchronous head and neck cancer primaries are an exception to this criterion and may qualify for the study.

8. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of MK-3475.

9. Currently receiving any other investigational agents or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of MK-3475.

10. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to MK-3475 or other agents used in the study.

11. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring systemic therapy, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, immunosuppression, autoimmune conditions, underlying pulmonary disease, or psychiatric illness/social situations that would limit compliance with study requirements.

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

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

14. Pregnant and/or breastfeeding. Patient must have a negative serum or urine pregnancy test within 72 hours of study entry.

15. Known history of active TB (bacillus tuberculosis).

16. Known history of hepatitis B (defined as hepatitis B survace antigen [HBsAg] reactive) or known active hepatitis C (defined as HCV RNA [qualitative] is detected) infection. Note: know testing for hepatitis B and hepatitis C is required unless mandated by local health authority.

17. Known history of HIV (HIV 1/2 antibodies).

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility by Washington University
2. Registration of patient in the Siteman Cancer Center Oncore database
3. Assignment of unique patient number (UPN)

Once the patient has been entered in the Siteman Cancer Center OnCore database, the WUSM coordinator will forward verification of enrollment and the UPN via email.

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below and scanning and emailing it to the research coordinator listed in the *Siteman Cancer Center Clinical Trials Core Protocol Procedures for Secondary Sites* packet at least one business day prior to registering patient:

1. Your name and contact information (telephone number, fax number, and email address)
2. Your site PI's name, the registering MD's name, and your institution name
3. Patient's race, sex, and DOB
4. Three letters (or two letters and a dash) for the patient's initials
5. Currently approved protocol version date
6. Copy of signed consent form (patient name may be blacked out)
7. Planned date of enrollment
8. Completed eligibility checklist, signed and dated by a member of the study team
9. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

Registrations may be submitted Monday through Friday between 8am and 5pm CT. Urgent late afternoon or early morning enrollments should be planned in advance and coordinated with the Washington University research coordinator. Registration will be confirmed by the research coordinator or his/her delegate by email within one business day. Verification of eligibility and registration should be kept in the patient chart.

All patients at all sites must be registered through the Siteman Cancer Center OnCore database at Washington University.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. Patients will also be identified by first, middle, and last initials. If the patient has no middle initial, a dash will be used on the case report forms (CRFs). All data will be recorded with this identification number on the appropriate CRFs.

5.0 TREATMENT PLAN

This is a phase II trial of neoadjuvant MK-3475 in locally advanced, surgically resectable HPV-negative HNSCC. After registration, tumor biopsy and peripheral blood will be obtained and then patients will receive preoperative MK-3475. Patients in Cohort 1 will receive a single dose of MK-3475 and will undergo surgery two to three weeks later. Blood and tissue will again be collected at the time of surgery, and paired pre-and post-treatment blood will be analyzed for changes in immune populations. Molecular approaches will be used to define alterations in peripheral blood immune populations and define a molecular signature of MK-3475 activity. Patients in Cohort 2 will receive two doses of neoadjuvant MK-3475 21 days apart (+/- 3 days). The second dose will be 14 to 24 days prior to surgery. Research blood and tissue will be collected at the time of surgery for Cohort 2 patients as well.

Patients will then proceed with postoperative adjuvant treatment (Section 5.3). After completing adjuvant treatment, patients in Cohort 1 with high-risk features per pathology (i.e. positive involved surgical margins or extracapsular extension, defined as extension of metastatic cancer cells beyond the lymph node capsule, including soft tissue metastasis which obliterates the entire lymph node or is present as small extranodal deposits of tumor in the neck soft tissues) will receive MK-3475 every 3 weeks for a maximum of 6 postoperative doses. MK-3475 will be started once the acute toxicities of post-operative chemotherapy and radiation have resolved to ≤ grade 1. Cohort 2 patients will be treated with standard adjuvant therapy but will not receive adjuvant MK-3475.

NOTE: Enrollment to Cohort 1 will continue until enrollment to Cohort 2 opens (or enrollment to Cohort 1 has been completed, whichever occurs first).

5.1 Premedication Administration

No premedications are required, but antiemetics may be given as per institutional practice if needed.

5.2 Agent Administration

MK-3475 will be given intravenously over the course of 30 minutes (-5 min/+10 min) on an outpatient basis at a dose of 200 mg. In Cohort 1, it will be given once prior to surgery (approximately 2 to 3 weeks pre-op). In cohort 2, a second dose of MK-3475 will be given 21 days (+/- 3) after dose 1 and 14-24 days before surgery. For patients in cohort 1 whose pathology displays high-risk features, MK-3475 will be given every 3 weeks after completion of standard of care adjuvant treatment (and after AEs resulting from adjuvant treatment have resolved to ≤ grade 1) for a maximum of 6 doses after surgery. The decision to administer chemotherapy or chemoradiation in the adjuvant setting is not dictated by this protocol, but should the treating physician choose to give adjuvant chemotherapy or chemoradiation, it will be given as described in Section 5.3. Patients in Cohort 2 will not be given adjuvant MK-3475.

5.3 Adjuvant Treatment

Intensity modulated radiation therapy (IMRT) is mandatory, and image-guided radiation therapy (IGRT) is recommended but optional. Chemotherapy will be high-dose bolus cisplatin. Non-local patients may receive adjuvant therapy at their local hospital provided a medical oncologist (if applicable) and radiation oncologist from the study team sign off on the treatment plan.

5.3.1 Radiation Therapy

5.3.1.1 Dose Specifications

The prescribed radiotherapy dose will be 60 Gy in 2 Gy once-daily fraction size (total of 30 fractions). Radiotherapy should begin on a Monday, Tuesday, or Wednesday. The daily dose of 2 Gy will be prescribed such that 95% of the PTV60 volume receives at least 60 Gy. As described below, PTV56 is also used, and PTV66 (given as an integrated boost) may be optionally defined. 3D-CRT followed by a 6 Gy boost is not permitted. Dose-limiting normal tissue constraints are listed below

5.3.1.2 Treatment Planning/Target Volumes

CTV60: This volume will receive 2 Gy per day. CTV60 will include the primary tumor bed (based on preoperative imaging, preoperative physical exam/endoscopy, operative findings, pathologic findings) plus regions of grossly involved lymphadenopathy. CTV60 may include the broader **operative resection bed** in the region of gross primary and nodal disease. The entire nodal regions in the involved hemi-neck may be included in CTV60 at the discretion of the investigator for perceived higher-risk cancers.

CTV60 will include the ipsilateral pathologically positive hemi-neck (if both sides of the neck are proven pathologically positive, CTV60 will include both sides). This generally means encompassing nodal levels 2a, 3, and 4 for most cases. Nodal levels 1, 2b, 5a, and 5b are included in CTV60 in selected circumstances. For example, level 1 should be included for oral cavity cancer but is not mandatory for

larynx cancer.

CTV56: This will include all other lesser risk regions in the operative bed (that were involved with surgery in any way) but felt to be at risk for harboring microscopic cancer that do not meet the criteria for CTV60. For example, this could apply to the broad operative bed, the contralateral hemi-neck being irradiated electively. This volume should not directly approach the skin < 5 mm. This volume will receive 1.85 Gy per day.

CTV66 (optional): This volume may be defined at the discretion of the treating radiation oncologist. This would include regions felt to be at particularly high risk for recurrence (e.g., an area of the ECS or positive margin of resection). **Note:** this area will be receiving a daily fraction size of 2.2 Gy and thus, the volume of CTV66 should be kept **as small as possible**.

Planning Target Volumes (PTVs): In general, the PTV should not extend beyond the skin surface, except if the skin was involved with tumor. If it does extend beyond the skin surface, the application of bolus material over this portion of the PTV may be considered. It is also allowable to define 2 PTVs for a given CTV: 1) PTV for planning, which extends beyond the skin surface and is used for planning treatment segments; and 2) PTV Evaluation (PTV_Eval), which does not reach the skin surface within 2 mm and is used for evaluation of the dose volume histogram to determine if treatment goals have been met.

PTV Expansion with and without Daily IGRT: The minimum CTV-to-PTV expansion should be 5 mm (a larger expansion may be necessary for a target volume subject to significant inter-fraction variability such as the tongue). In general, the CTV-to-PTV expansion should not exceed 10 mm.

Management of the Low Neck/Supraclavicular Region (Match vs. No Match for IMRT Treatment Modality): It is recognized that comprehensive head and neck irradiation incorporating IMRT can be done in 1 of 2 ways, either of which is permitted for this study.

1) Match: the upper cervical lymphatics and primary tumor bed are treated with IMRT. The lower cervical lymphatics and supraclavicular region are treated with a single AP (or occasionally APPA for larger patients with posterior neck at high risk) non-IMRT technique. The latter non-IMRT field(s) is matched the upper neck IMRT fields. This technique also allows for a simultaneous blocking of portions of the larynx, hypopharynx, and cervical esophagus in the lower neck fields. In general, this technique is appropriate for irradiation of cancers of the oral cavity or oropharynx.
2) No Match: The entire clinical target volume (CTV) [upper and lower neck and primary tumor bed] is irradiated with IMRT. There is no match line between upper and lower portions of the regions at risk. In this technique, limiting radiotherapy dose to organs at risk (OARs), e.g. the cervical esophagus, is entirely achieved by inverse treatment planning via IMRT algorithms. This technique in general is appropriate for irradiation of

cancers of the larynx and/or oral/pharyngeal cancers that involve the hypopharynx.

Dose to Supraclavicular Nodal Region: Regardless of whether technique 1 (Match) or technique 2 (No Match) is used, the dose to the supraclavicular nodal region may be limited to 56 Gy for the non-operated, node negative hemi-neck, and for an involved hemi-neck if level 4 nodes were dissected and found to be negative.

IMRT Dose Prescription to PTVs: The prescribed radiotherapy dose will be 60 Gy in 2 Gy once-daily fraction size 5 days a week. For inverse planning IMRT, the goal is for 95% of the PTV60 to receive ≥ 2 Gy with a minimum dose (cold spot) of no less than 56 Gy. It is recognized that portions of the PTV close to the skin may receive significantly less than 56 Gy.

Prioritization for IMRT Planning

1. Spinal cord
2. Brainstem
3. PTV60
4. PTV56 (required if applicable)
5. PTV66 (if applicable)
6. OARpharynx
7. Parotid gland contralateral to primary tumor site
8. GSL
9. Esophagus
10. Lips
11. Oral Cavity
12. Parotid gland ipsilateral to primary tumor site
13. Unspecified tissue outside the targets

5.3.1.3 Definitions and Constraints for Normal Tissues / Organs at Risk (OARs)

Spinal Cord: The cord begins at the cranial-cervical junction (i.e., the top of the C1 vertebral body). Superior to this is brainstem and inferior to this is cord. The inferior border of the spinal cord is at approximately T3-4 (i.e., just below the lowest slice level that has PTV on it). The spinal cord shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) spinal cord shall be defined. The PRVcord = cord + 5 mm in each dimension. 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 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. For non-oral cavity cancers, the oral cavity will be defined as a composite structure consisting of the anterior half to two-thirds of the oral tongue/floor of mouth, buccal mucosa, and palate. For oral cavity cancers, the oral cavity will be defined as the subset of this composite structure that does not overlap with PTV.

Parotid Glands: Parotid glands will be defined in their entirety (superficial and deep lobes) based on the treatment planning CT scan. Parotid gland volume may include portions of any of the CTVs if the primary or nodal volumes involved or closely approached the parotid, although they can overlap the PTVs.

OARpharynx: This will be defined as the "uninvolved" posterior pharyngeal wall plus adjacent constrictor muscles. This extends from the superior constrictor region (the inferior pterygoid plates level) to the cricopharyngeal inlet (posterior cricoid cartilage level). This should not overlap the PTVs.

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

Glottic/Supraglottic Larynx (GSL): Obviously, for patients who have had a total laryngectomy, this structure is not applicable. This will be defined as a "triangular prism-shaped" volume that begins just inferior to the hyoid bone and extends to the cricoid cartilage inferiorly and extends from the anterior commissure to include the arytenoids. This includes the infrahyoid but not suprahyoid epiglottis.

Mandible: This includes the entire boney structure of the mandible from TMJ through the symphysis. It is recognized that for oral cavity cancers, this may overlap with CTVs and PTVs.

Unspecified Tissue outside the Targets: This will be defined as tissue located between the skull base and thoracic inlet.

IMRT Dose Constraints to Normal Structures

All of the following structures are to be contoured:

- Spinal cord: the PRVcord should not exceed 48 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). The spinal cord PRV should not exceed 50 Gy to any volume in excess of 0.01 cc. In treatment planning, the spinal cord PRV should be given the highest priority.
- Brainstem: the PRVbrainstem should not exceed 52 Gy to any volume in excess of 0.03 cc. In treatment planning, the PRVbrainstem should be given less priority than the PRVcord but more priority than the other critical structures listed below.
- Lips: reduce the dose as much as possible. The mean dose should be < 20 Gy. For non-oral cavity cancers, the maximum dose will be < 30 Gy. For oral cavity cancers, the maximum dose will be < 50 Gy.
- Oral cavity: reduce the dose as much as possible. For non-oral cavity cancers, the mean dose should be 30 Gy. Efforts should be made to avoid

hot spots (> 60 Gy) within the oral cavity, particularly for non-oral cavity cancers.

- Parotid glands: in many cases, it may 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 up to 30 Gy.
- OARpharynx: reduce the dose as much as possible. Some recommended (but not mandatory) treatment goals include: 1) no more than 33% of the OARpharynx exceeds 50 Gy; 2) mean dose < 45 Gy; 3) no more than 15% of the OARpharynx exceeds 60 Gy.
- Cervical esophagus: reduce the dose as much as possible. For oral or oropharyngeal cancer, some recommended (but not mandatory) treatment goals include: 1) no more than 33% of the esophagus exceeds 45 Gy; 2) mean dose < 35 Gy; 3) no more than 15% of the esophagus exceeds 54 Gy. For larynx cancer, higher doses are expected and permitted. Some recommended (but not mandatory) treatment goals include: 1) no more than 33% of the esophagus exceeds 50 Gy; 2) mean dose < 45 Gy; 3) no more than 15% of the esophagus exceeds 60 Gy.
- Glottic and supraglottic larynx: reduce the dose as much as possible. In patients with resected oral or oropharyngeal carcinoma, it is recommended that the dose to the larynx should be kept < 45 Gy whenever feasible.
- Mandible: reduce the dose as much as possible. It is recognized that particularly for oral cavity cancers, significant portions of the mandible will overlap the CTVs and/or PTVs; however, hot spots within the mandible should be avoided. It is recommended that maximum dose within the mandible be < 66 Gy.
- Unspecified tissue outside the targets: for the typical case in which there is no CTV66, no more than 0.03 cc can receive 66 Gy or more. When a boost is used to increase the dose to high-risk regions to as much as 66 Gy, these numbers can be increased. In this case, no more than 0.03 cc of the unspecified dose should exceed the boost dose value plus 10% or 72.6 Gy.

5.3.1.4 Compliance Criteria

Treatment breaks must be clearly indicated in the treatment record, along with the reasons for the breaks. Treatment breaks, if necessary, ideally should not exceed five treatment days at a time and ten treatment days total. Treatment breaks should only be allowed for resolution of severe acute toxicity and/or for intercurrent illness and not for social or logistical reasons. Any treatment breaks exceeding two treatment days for reasons other than toxicity/illness will be considered a protocol deviation.

It is recommended that patients receive BID treatments with minimum 6-hour inter-fraction interval to compensate for missed days included holidays and those for toxicity or illness once sufficiently recovered with the goal of keeping the overall treatment time confined to 6 weeks or 45 consecutive days.

	Per Protocol	Variation Acceptable
Total RT dose to PTV60 (to 95% of PTV60)	60-64 Gy	< 60 and ≥ 58 Gy or > 64 and ≤ 66 Gy
Minimum dose for a volume of 0.03 cc ("cold spot" within PTV60, not including portion of PTV near (<8 mm) skin)	≥ 56 Gy	≥ 54 and < 56 Gy
Maximum dose (hot spot) within PTV60* for a volume of 0.03 cc	≤ 69 Gy	> 69 and ≤ 72 Gy
Maximum dose (hot spot) outside of PTV60 for a volume of 0.03 cc	≤ 66 Gy	> 66 and ≤ 70 Gy
Total RT dose to PTV 56 (to 95% of PTV56)	56-58 Gy	< 56 and ≥ 53.2 Gy or > 58 and ≤ 60 Gy
Minimum dose (cold spot) within PTV56 for a volume of 0.03 cc	45 Gy	40 Gy
Total RT dose to PTV 66 (to 95% of PTV66)	66-68 Gy	< 66 and ≥ 62.7 Gy or > 68 and ≤ 70.6 Gy
Minimum dose (cold spot) within PTV 66 for a volume of 0.03 cc	61.4 Gy	59 Gy
Maximum dose (hot spot) within PTV66	1. No more than 20% of PTV66 is at or above 72.6 Gy 2. No more than 0.03 cc of PTV66 can go above 75.9 Gy	1. No more than 40% of PTV66 is at or above 72.6 Gy 2. No more than 0.03 cc of PTV66 can go above 78 Gy
Total RT dose to spinal cord PRV (0.03 cc)	< 48 Gy	≥ 48 but ≤ 50 Gy
Total RT dose to brainstem PRV (0.03 cc)	≤ 50 Gy	> 50 Gy and < 52 Gy
Lips maximum dose to 0.03 cc for non-oral cavity cancers	≤ 25 Gy	≤ 30 Gy
Lips maximum dose to 0.03 cc for oral cavity cancers	≤ 45 Gy	≤ 50 Gy
Oral cavity (for non-oral cavity cancers) mean dose	≤ 30 Gy	> 30 but ≤ 35 Gy
Parotid gland: mean dose to individual parotid gland	< 26 Gy	> 26 Gy and < 30 Gy
Overall RT treatment time	< 45 days	≥ 45 and ≤ 50 days**
Non-medically indicated treatment interruptions	0-2	3-4

* Not including the region of PTV60 that falls within PTV66 (if applicable)
** Deviation unacceptable: > 50 days (without a medially appropriate indication for delay)

5.3.2 Chemotherapy

Patients will receive cisplatin, 100 mg/m^2, administered intravenously on Days 1,22, and 43 of the treatment course (Note: cisplatin given within 24 hours of Days 1, 22, and 43 due to holidays, for example, is acceptable).

Use the actual body weight as long as the BSA is ≤ 2.0. **If the BSA is > 2.0, recalculate using the ideal weight, and use the recalculated BSA to determine the dose with no cap or use a cap with a BSA of 2.0, whichever is higher**. Use the formulas below:

Males (kg): 51.65 + (1.85 x (height [inches] – 60))
Females (kg): 48.67 + (1.85 x (height [inches] – 60))

High dose cisplatin is a highly emetogenic regimen with significant incidence of delayed nausea and vomiting. Institutional guidelines for highly emetogenic regimens should be followed.

Patients must receive vigorous hydration and diuresis. A suggested regimen is prehydration with a 1 liter of D5N S over 2-4 hours and mannitol, 12.5 g *i.v.* bolus immediately prior to cisplatin. Then cisplatin, 100 mg/m^2, in 500 ml NS is administered over 1-2 hours with an additional 1 to 1.5 liters of fluid given post-hydration. Any pre-existing dehydration must be corrected prior to cisplatin administration. Should extravasation occur, the treating physician should follow institutional guidelines for management.

5.3.2.1 Dose Modifications for Cisplatin, Day 22 and Day 43

Neutropenia: If on the day of scheduled treatment with cisplatin the absolute neutrophil count (ANC) is < 1000, hold treatment until ANC ≥ 1000, then treat at 100% dose. Neutropenic fever will require permanent 25% dose reduction. Neulasta may be used in the instance of neutropenia or neutropenic fever.

Thrombocytopenia: If on the day of scheduled treatment with cisplatin the platelet count is < 75,000, hold treatment until platelets are > 75,000, then treat at 100% dose. Thrombocytopenia that results in bleeding will require a 25% dose reduction.

Neurotoxicity: If any signs of grade 3 or greater neurotoxicity occur, discontinue cisplatin. Continue RT.

Renal Adverse Events: Cisplatin should be administered on the scheduled day of treatment using the following guidelines:

Note: If creatinine is > 1.5 mg/dl, clearance must be done in order to make dose adjustment.

Creatinine Clearance Cisplatin Dose
> 50 ml/min. 100 mg/m^2
40-50 ml/min. 50 mg/m^2
< 40 ml/min. Discontinue

Other Adverse Events:

- Mucositis: Grade 4 will require a 25% dose reduction
- Ototoxicity: For new clinical hearing loss not requiring a hearing aid or for

tinnitus that interferes with activities of daily living, treat at 50% dose reduction. For hearing loss requiring a hearing aid, discontinue cisplatin. Continue RT.

If the second or third dose of cisplatin is delayed more than 7 days because of hematologic or renal adverse events, that dose will be omitted.

If a weight change of ≥ 10% occurs, the cisplatin dose should be adjusted.

5.4 Definition of Evaluability

Patients must receive at least one postoperative dose of MK-3475 in order to be considered evaluable for the primary objective.

5.5 General Concomitant Medication and Supportive Care Guidelines

All treatments that the investigator considers necessary for a patient's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

Patients are prohibited from receiving the following therapies while in screening for and enrolled in this trial:

- Anti-cancer systemic chemotherapy other than as dictated in the post-operative setting or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than MK-3475
- Radiation therapy other than as dictated in the post-operative setting
- Live vaccines within 30 days prior to the first dose of 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. Steroids may be used as anti-emetics around the time of chemotherapy delivery, which may occur more than 10 weeks after the pre-operative single dose MK-3475 and 4 weeks before post-operative dosing. In the immediate perioperative period patients receive steroids to help with wound edema from surgery. The use of physiologic doses of corticosteroids may be approved.

5.5.1 Supportive Care Guidelines for Infusion Reactions

Pembrolizumab may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. The table below shows treatment guidelines for patients who experience an infusion reaction associated with MK-3475.

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 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 (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.6 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative serum or urine pregnancy test within 72 hours prior to the first dose of MK-3475.

Pembrolizumab may have adverse effects on a fetus in utero.

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

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below). Women in the following categories are not considered of childbearing potential:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
    Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

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

<u>Male Participants</u>:
Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined timeframe:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in the table below when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
  - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below during the protocol-defined timeframe.

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of < 1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen-containing) hormonal contraception [b, c] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b, c] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least [X days, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment. c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test.

Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected, after the last dose of study treatment, and as required locally.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

5.7 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms. In the absence of treatment delays due to adverse events, treatment may continue for up to 6 doses of MK-3475 following surgery or until one of the following criteria applies:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious non-compliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will be followed as indicated in the study calendar.

5.8 Duration of Follow-up

All patients will be followed for at least 4 years for cancer surveillance following completion of postoperative treatment with MK-3475 (i.e. up to 5 years after surgery) or for 5 years after surgery for patients who did not receive post-op MK-3475 or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event or up to 5 years as dictated by the treating physician.

6.0 DOSE DELAYS/DOSE MODIFICATIONS

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in the table below.

General instructions:

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

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent grade 2	Permanently discontinue		
Diarrhea / colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (i.e. diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with 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.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	

Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or Permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g. levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

Please also refer to Section 5.5 for information regarding supportive care and possible dose adjustments.

7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outline below.

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 7.2.

The FDA requires that all serious and unexpected adverse events be reported as outlined in Section 7.6. In addition, any fatal or life-threatening adverse experiences where there is a reasonable possibility of relationship to study intervention must be reported.

Merck requires that any SAE and SUSAR information be reported as outlined in Section 7.7, as well as events of clinical interest (Section 7.7.2).

7.1 Definitions

7.1.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

For Merck's purposes, an adverse event (or "AE") shall mean any untoward medical occurrence in a Study subject who is administered the Study Drug regardless of whether or not a causal relationship with the Study Drug exists. By way of example and without limitation, an AE can be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of the Study Drug.

7.1.2 Serious Adverse Event (SAE)

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

All unexpected SAEs must be reported to the FDA.

For Merck's purposes, a serious adverse event (or "SAE") shall mean any untoward medical occurrence in a Study subject who is administered the Study Drug that results in death, a life-threatening drug experience, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect, cancer, or is a new cancer if the cancer is the condition of the study, or overdose. Other important medical events that may jeopardize the patient or may require intervention to prevent one of the outcomes listed previously should also be considered "serious."

7.1.3 Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

Events that are both serious AND unexpected must be reported to the FDA.

7.1.4 Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Life-threatening adverse experiences must be reported to the FDA.

7.1.5 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm

(including physical, psychological, economic, or social harm) than was previously known or recognized.

7.1.6 Suspected Unexpected Serious Adverse Reaction

Suspected Unexpected Serious Adverse Reaction (or "SUSAR") shall mean any serious adverse event (defined in Section 7.1.2), the nature, severity or frequency of which is not consistent with information in the most current investigator's brochure, or with respect to a marketed product the most current Summary of Product Characteristics (SPC) or Package Insert.

7.1.7 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

7.1.8 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

7.1.9 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Local IRB pre-approval of all protocol exceptions must be obtained prior to the event. For secondary sites, the Washington University PI will issue approval of the exception, but it must also be submitted to the local IRB with documentation of approval forwarded to Washington University. Washington University IRB approval is not required for protocol exceptions occurring at secondary sites.

7.2 Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or

notification to the PI of the event.

7.3 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to a QASMC auditor.

7.4 Reporting Requirements for Secondary Sites

The research team at each secondary site is required to promptly notify the Washington University PI and research coordinator of all reportable events (as described in Section 7.6) within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event. This notification may take place via email if there is not yet enough information for a formal written report (using either an FDA MedWatch form if required or an institutional SAE reporting form if not). A formal written report must be sent to the Washington University PI and research coordinator within **10 working days** of the occurrence of the event or notification of the secondary site's PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event.

The research team at a secondary site is responsible for following its site's guidelines for reporting applicable events to its site's IRB according to its own institutional guidelines. The research team at Washington University is responsible for reporting all applicable events to the FDA.

7.5 Reporting to Secondary Sites

The Washington University PI (or designee) will notify the research team at each secondary site of all reportable events that have occurred at other sites within **10 working days** of the occurrence of the event or notification of the PI of the event. This includes events that take place both at Washington University and at other secondary sites, if applicable.

7.6 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the Washington University principal investigator to report any unanticipated problem to the FDA as follows:

- Report any unexpected fatal or life-threatening adverse experiences (Section 7.1.4) associated with use of the drug (i.e., there is a reasonable possibility that the experience may have been caused by the drug) by telephone or fax no later than **7 calendar days** after

initial receipt of the information.

- Report any serious, unexpected adverse experiences (Section 7.1.2), as well as results from animal studies that suggest significant clinical risk within **15 calendar days** after initial receipt of this information.

All MedWatch forms will be sent by the investigator or investigator's team to the FDA at the following address or by fax:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products
5901-B Ammendale Rd.
Beltsville, MD 20705-1266
FAX: 1-800-FDA-0178

Secondary sites must submit a completed MedWatch form to the Washington University PI and research coordinator within **4 calendar days** (for fatal or life-threatening adverse experiences) or **11 calendar days** (for serious, unexpected adverse experiences). The Washington University PI will be responsible for submitting all MedWatch forms from secondary sites to the FDA within the timeframes specified above.

7.7 Reporting to Merck & Co., Inc.

The PI shall forward to Merck's Global Safety group (FAX 215-661-6229) any SAE and SUSAR information, including, but not limited to, all initial and follow-up information involving any study subject in the study within 2 business days or 3 calendar days (whichever comes first) of learning of the SAE or SUSAR. Only SAEs that are believed to be related to the use of MK-3475 will be reported to Merck.

7.7.1 Reporting Overdose

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

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide

Product Safety; FAX 215 661-6229)

7.7.2 Reporting Pregnancy and Lactation

Although pregnancy and infant exposure during breastfeeding 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) that occurs during the trial.

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

Pregnancies and infant exposures during breastfeeding that occur from the time of treatment allocation/randomization through 120 days following cessation of MK-3475, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies 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).

7.7.3 Reporting Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported 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 that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is ≥ 3 x IULN and an elevated total bilirubin lab value that is ≥ 2 x IULN and, at the same time, an alkaline phosphatase lab value that is < 2 x IULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

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

7.8 Timeframe for Reporting Required Events

For patients who do not receive adjuvant pembrolizumab, adverse events will be tracked for 30 days following date of surgery. For patients who do receive adjuvant MK-3475, adverse events will be tracked for 30 days after the last dose of MK-3475. For the purposes of this protocol, reportable adverse events are events thought to be possibly, probably, or definitely related to MK-3475. Events thought to be probably or definitely related to surgery, adjuvant chemotherapy, or radiotherapy need not be recorded. Please note that patients must be followed for events of clinical interest for 90 days following the last dose of MK-3475 for all patients.

8.0 PHARMACEUTICAL INFORMATION

8.1 MK-3475

8.1.1 MK-3475 Description

MK-3475 is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, MK-3475 has high affinity and potent receptor blocking activity for PD-1. MK-3475 has an acceptable preclinical safety profile and is being advanced for clinical development as an IV immunotherapy for advanced malignancies.

8.1.2 Clinical Pharmacology

Refer to Section 5.2 of the IB.

8.1.3 Pharmacokinetics and Drug Metabolism

Refer to Section 5.2 of the IB.

8.1.4 Supplier

MK-3475 will be provided free of charge by Merck & Co., Inc.

8.1.5 Dosage Form and Preparation

Merck will provide MK-3475 as a liquid drug product.

8.1.6 Storage and Stability

MK-3475 should be stored under refrigerated conditions (2°C - 8°C).

If not used immediately, vials and/or IV bags may be stored at 2-8 °C for up to a cumulative time of 20 hours. If refrigerated, the vials and/or IV bags should be allowed to equilibrate to room temperature prior to subsequent use. MK-3475 solutions may be stored at room temperature for a cumulative time of up to 4 hours.

8.1.7 Administration

MK-3475 will be given intravenously over the course of 30 minutes (-5 min/+10 min) on an outpatient basis.

9.0 CORRELATIVE STUDIES

9.1 Tumor Biopsy

9.1.1 Collection of Specimens

Two 3.5 mm punch biopsies of the primary site will be taken at baseline. If the participant is enrolled in Washington University's TAP protocol (the head & neck bank, HRPO# 201102323), tissue that has been banked may be accessed in lieu of fresh biopsy at baseline. Tissue from the surgical resection (preferred sometime between Day 14-17 inclusive but may occur up to Day 24 depending on timing of surgery) will also be harvested for analysis of intratumoral changes.

9.1.2 Handling of Specimens

Specimens collected at WUSM will be transported fresh to the Immunomonitoring Lab on the 7th floor of the BJC Institute of Health, WUSM for lymphocyte extraction on the samples. Additionally, some samples will be sent to the Tissue Procurement Core on the 5th floor of the BJC Institute of Health, WUSM. Samples collected at DFCI will be transported fresh to Dr. Uppaluri's lab. The samples will be used for genomic (RNA/DNA) analysis and will be transplanted into immunodeficient NSG mice (NOD/scid/gamma chain knockout) and engraftment will be monitored. Tumors established in mice will be used to generate cell lines and divided into ones that were responsive or unresponsive to MK-3475 treatment. Specimens from WUSM may be shipped to DFCI, and specimens from DFCI may be shipped to WUSM. Shipping instructions will be provided at a later date.

9.2 Archival Tissue

Access to paraffin blocks from all patients enrolled to this study will be requested. Blocks may be analyzed at WUSM or at DFCI.

Hematoxylin and eosin-stained slides of formalin-fixed paraffin-embedded (FFPE) tissues will be digitized to apply a machine learning algorithm to quantify tumor infiltrating lymphocyte infiltration as a potential predictor of response. FFPE blocks may be used to create tissue microarrays (TMAs) for multiplex histological analysis.

9.3 Peripheral Blood for Biomarkers

9.3.1 Collection of Specimens

Blood (30 mL) will be collected in 3 purple top EDTA tubes at the following time points, for both Cohort 1 and Cohort 2:

- Baseline
- Time of surgery (between Day 14 and Day 24 inclusive)
- 3 months post-surgery6 months post-surgery
- 9 months post-surgery
- 12 months post-surgery

9.3.2 Handling of Specimens

A portion of each sample will be stored as buffy coat peripheral blood mononuclear cells (PBMC) or DNA/RNA for future studies. This will take place in the BJC Institute of Health at WUSM and Dr. Uppaluri's lab at DFCI. Specimens from WUSM may be shipped to DFCI, and specimens from DFCI may be shipped to WUSM. Shipping instructions will be provided at a later date.

10.0 STUDY CALENDAR

10.1 Calendar for Cohort 1

NOTE: Enrollment to Cohort 1 will continue until enrollment to Cohort 2 opens (or enrollment to Cohort 1 has been completed, whichever occurs first).

	Screening[9]	Baseline	Day 1	Days 14-24 (Surgery)	Adjuvant CRT[5]	3 Mos after Surgery	6 Mos after Surgery	9 Mos after Surgery	12 Mos after Surgery	Follow-Up[4]
Informed consent	X									
H&P, ECOG PS, wt	X		X							
CBC	X		X							
CMP	X		X							
Coagulation panel[1]	X									
Pregnancy test[2]	X[3]									
T3, FT4, and TSH	X									
Urinalysis	X									
Tumor biopsy		X		X						
Research blood		X		X		X[8]	X[8]	X[8]	X[8]	
MK-3475			X							
RT					X[6]					
Cisplatin					X[7]					
Neck CT	X			X[10]		Following completion of adjuvant treatment, routine imaging will take place approximately every 3 months for the first 15 months then approximately every 6 months thereafter.				
Chest CT or PET/CT	X									
AE assessment		X	Patients will be followed for AEs for 30 days after surgery or last dose of adjuvant MK-3475, and for Events of Clinical Interest for 90 days following the last dose of MK-3475							

1. Consisting of a PTT and PT/INR
2. Women of childbearing potential only
3. No more than 72 hours prior to start of treatment
4. Follow-up will be performed as per routine care (every 2-3 months for 15 months, then every 5-6 months) and data on recurrence and survival will be recorded.
5. Adjuvant therapy should typically begin between 4 and 6 weeks following surgery. Laboratory assessments will be performed as per routine care and will not be dictated by this research protocol.
6. RT will be given as 30 daily fractions and should start on a Monday, Tuesday, or Wednesday. Refer to Section 5.3.1 for guidelines.
7. High-dose cisplatin will be given on Days 1, 22, and 43 (+/- 1 day).
8. +/- 7 days, or drawn with standard labs
9. Screening exams must take place within 14 days prior to registration with the exception of imaging, which must take place within 30 days prior to registration.
10. After neoadjuvant pembrolizumab but before surgery.

10.2 Calendar for Cohort 2

	Screening[9]	Baseline	Day 1	Day 22 (+/-3)	14-24 Days Post Day 22 (Surgery)	Adjuvant CRT[5]	3 Mos after Surgery	6 Mos after Surgery	9 Mos after Surgery	12 Mos after Surgery	Follow -Up[4]
Informed consent	X										
H&P, ECOG PS, wt	X		X								
CBC	X		X								
CMP	X		X								
Coagulation panel[1]	X										
Pregnancy test[2]	X[3]										
T3, FT4, and TSH	X										
Urinalysis	X										
Tumor biopsy		X			X						
Research blood		X			X		X[8]	X[8]	X[8]	X[8]	
MK-3475			X	X							
RT						X[6]					
Cisplatin						X[7]					
Neck CT	X				X[10]		Following completion of adjuvant treatment, routine imaging will take place approximately every 3 months for the first 15 months then approximately every 6 months thereafter.				
Chest CT or PET/CT	X										
AE assessment		X		Patients will be followed for AEs for 30 days after surgery or last dose of adjuvant MK-3475, and for Events of Clinical Interest for 90 days following the last dose of MK-3475							

1. Consisting of a PTT and PT/INR
2. Women of childbearing potential only
3. No more than 72 hours prior to start of treatment
4. Follow-up will be performed as per routine care (every 2-3 months for 15 months, then every 5-6 months) and data on recurrence and survival will be recorded.
5. Adjuvant therapy should typically begin between 4 and 6 weeks following surgery. Laboratory assessments will be performed as per routine care and will not be dictated by this research protocol.
6. RT will be given as 30 daily fractions and should start on a Monday, Tuesday, or Wednesday. Refer to Section 5.3.1 for guidelines.
7. High-dose cisplatin will be given on Days 1, 22, and 43 (+/- 1 day).
8. +/- 7 days, or drawn with standard labs
9. Screening exams must take place within 14 days prior to registration with the exception of imaging, which must take place within 30 days prior to registration.
10. After second dose of neoadjuvant pembrolizumab but before surgery.

10.3 Post-CRT Calendar for Cohort 1 Participants Who Receive Adjuvant MK-3475

Only patients whose pathology shows high risk features will receive further treatment with MK-3475. This treatment will start 1-3 months after the end of standard of care adjuvant treatment. Each visit has a window of +/- 3 days.

	Dose #1	Dose #2	Dose #3	Dose #4	Dose #5	Dose #6
CBC	X	X	X	X	X	X
CMP	X	X	X	X	X	X
T3, FT4, and TSH	X		X		X	
Urinalysis	X		X		X	
MK-3475[1]	X	X	X	X	X	X
Neck CT	Routine imaging will take place approximately every 3 months for the first 15 months following completion of adjuvant treatment, and approximately every 6 months thereafter.					
Chest CT or PET/CT						
AE assessment	X ---------- X					

1. MK-3475 is given Q3W in the adjuvant setting.

11.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form Tumor Biopsy Form Research Blood Form Archival Tissue form	Prior to starting treatment
Study Drug Form	Every dose of MK-3475
Tumor Biopsy Form Research Blood Form	Time of surgery
Chemoradiation Form	End of CRT
Research Blood Form	3, 6, 9, and 12 months post-surgery (as applicable per cohort and adjuvant treatment eligibility)
Adverse Events Form	Continuous
Treatment Summary Form	Completion of treatment
Follow Up Form	5 years after end of treatment
MedWatch Form	See Section 7.0 for reporting requirements

12.0 MEASUREMENT OF EFFECT

12.1 Methods for Evaluation of LRR/DM

All measurements should be taken and recorded in metric notation using a ruler or calipers. All

baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy: There is a strong likelihood of utilization of endoscopic techniques in this head and neck cancer clinical trial. Again as the head and neck region is easily accessible, endoscopic measurements may be used.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: FDG-PET is part of the post-operative surveillance for advanced head and neck cancers. The measurement of SUVmax in pre-treatment and post-treatment scans will be used as the secondary endpoint.

12.2 RECIST Analysis of Post-Neoadjuvant Dose CT Scan for Treatment Response

For new patients recruited to this study beginning with Amendment #5, we will also perform a study supported head and neck dedicated CT with contrast.

12.2.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be evaluated for response on Day 14-24 after the infusion of study drug just prior to surgery.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.2.2 Disease Parameters

Measurable disease: By definition, all patients will have measurable lesions (at least 20 mm in the longest diameter) as measured by calipers on clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters)..

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

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Any distant metastatic disease would exclude patient enrollment and by definition as also considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

13.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Data and Safety Monitoring Committee (DSMC) will be specifically convened for this trial to review toxicity data at least every 6 months following the activation of the first secondary site. A DSMC will consist of no fewer than 3 members including 2 clinical investigators and a biostatistician. Like investigators, DSMC members are subject to the Washington University School of Medicine policies regarding standards of conduct. Individuals invited to serve on the DSMC will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials, in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMC must also be disclosed.

The DSM report will be prepared by the study statistician with assistance from the study team, will be reviewed by the DSMC, and will be submitted to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC). This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual including numbers from participating sites
- Protocol activation date at each participating site
- Average rate of accrual observed in year 1, year 2, and subsequent years at each participating site
- Expected accrual end date and accrual by site
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules

- Summary of toxicities at all participating sites
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

Further DSMC responsibilities are described in the DSMC charter.

Until such a time as the first secondary site activates this protocol, a semi-annual DSM report to be prepared by the study team will be submitted to the QASM Committee beginning 6 months after study activation at Washington University.

The study principal investigator and coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines (please refer to Section 7.0).

Refer to the Washington University Quality Assurance and Data Safety Monitoring Committee Policies and Procedures for full details on the responsibilities of the DSMC at https://siteman.wustl.edu/wp-content/uploads/2015/10/QASMC-Policies-and-Procedures-03.31.2015.pdf

14.0 AUDITING

As coordinating center of this trial, Washington University (via the Quality Assurance and Safety Monitoring Committee (QASMC) will monitor each participating site to ensure that all protocol requirements are being met; that applicable federal regulations are being followed; and that best practices for patient safety and data collection are being followed per protocol. Participating sites will be asked to send copies of all audit materials, including source documentation. The audit notification will be sent to the Washington University Research Patient Coordinator, who will obtain the audit materials from the participating institution.

Notification of an upcoming audit will be sent to the research team one month ahead of the audit. Once accrual numbers are confirmed, and approximately 30 days prior to the audit, a list of the cases selected for review (up to 10 for each site) will be sent to the research team. However, if during the audit the need arises to review cases not initially selected, the research team will be asked to provide the additional charts within two working days.

Items to be evaluated include:

- Subject screening and enrollment
- Reporting of adverse events
- Maintenance of HIPAA compliance
- Completeness of regulatory documentation
- Completeness of participant documentation
- Acquisition of informed consent
- IRB documentation
- Issues of protocol adherence

Additional details regarding the auditing policies and procedures can be found at https://siteman.wustl.edu/wp-content/uploads/2015/10/QASMC-Policies-and-Procedures-03.31.2015.pdf

15.0 STATISTICAL CONSIDERATIONS

15.1 Sample Size Justification

15.1.1 Original (Cohort 1)

Historical clinical trial data from the Cooper et al. and Bernier et al. studies (1, 2) showed that 35% of patients undergoing multimodality treatment for locally advanced "high risk" HNSCC suffer from LRR and DM at one year. Our primary endpoint in the proposed single arm trial is to reduce LRR/DM to 15%. We estimate that 31 patients will be needed to allow us to detect with 80% power ($\alpha = 0.05$) a difference of at least 20% in the one-year LRR/DM rate. Since 80% of the patients are classified as high-risk post-surgery, and taking into account a 15% drop-out rate observed in most of our studies, we estimate that we will need to recruit 46 patients for this study to be able to achieve the goal of 31 evaluable subjects successfully completing the study. As stated earlier in Section 1.8, the original hypothesis of the protocol was that adjuvant MK-3475 would reduce the LRR/DM rate in patients with high risk pathology features; however, the unexpectedly low rate of patients with high risk pathology features and thus low number of patients given adjuvant MK-3475 coupled with the absence of LRR/DM events to date make it impossible to prove the original hypothesis in such a small study.

15.1.2 Amendment #6 (Addition of Cohort 2)

In Cohort 2, we hypothesize that two doses of neoadjuvant MK-3475 will result in a major pathologic treatment effect in 50% of patients compared to the rate of 25% seen in Cohort 1 treated with one neoadjuvant dose of MK-3475. We estimate that a sample size of 26 patients in Cohort 2 is needed to allow us to detect with 80% power at the one-sided alpha level of 0.05 a major pathologic treatment rate of 50%, as a significant improvement over the 25% rate in Cohort 1. Considering a 15% drop out rate, we plan to enroll 31 patients in Cohort 2.

NOTE: Enrollment to Cohort 1 will continue until enrollment to Cohort 2 opens (or enrollment to Cohort 1 has been completed, whichever occurs first).

15.2 Analysis

15.2.1 Relapse Rates and Adverse Events

Relative frequency will be used to report the one-year rate of LRR/DM. A one sample binomial test will be used to test the null hypothesis that LRR/DM rate is significantly different from 0.35. Confidence intervals of 95% around the point estimate for the proportion rate of LRR/DM will be calculated and the upper limit will be compared to 0.35.

We will record and report all side effects and adverse events observed in the study as described above. Paired samples t-test will be used to compare the anti-HNSCC immune response before and after MK-3475.

15.2.2 Long Term Relapse Rates and Survival Outcomes

On long-term follow-up analysis, two-year rates of LRR/DM will be assessed, and LRR/DM rates will be compared between Cohorts 1 and Cohorts 2 and between patients who experienced pathologic treatment response (pTR) to those who did not. Fisher's exact and chi-square testing will be used to test the null hypothesis that LRR/DM rates are not significantly different between cohorts and between patients with versus without pTR following neoadjuvant MK-3475.

Overall and event-free survival will be analyzed using Kaplan Meier methods in our overall patient population. Kaplan Meier survival curves will then be stratified (1) by cohort, (2) by pTR status or (3) by presence of recurrent genomic alterations to assess differences in overall and event-free survival. Log-rank tests will be used to compare survival between groups at a significance level of 0.05.

We will assess pathologic responses in lymph nodes versus in the primary tumor in isolation as a predictor of overall and event-free survival. There is evidence from neoadjuvant immunotherapy trials in lung cancer that pathologic response in lymph nodes may be an independent predictor of survival (34).

15.2.3 Machine Learning Histopathologic Spatial Analysis

Utilizing a previously developed machine-learning classifier trained on pathologist-labeled samples that identifies tumor cells and tumor-infiltrating lymphocytes (TIL) across digitized slides, we will quantify the extent of TIL infiltration by measuring multitype nearest neighbor distances (G-cross function) comparing the coordinates of lymphocytes to tumor cells. Levels of spatial infiltration within tumor biopsy slides are then outputted as G-cross(r) curves, and the area-under-the-curve is used as a metric for measuring TIL spatial infiltration (G-score). A higher G-score is representative of a higher degree of TIL infiltration.

For this study, we aim to use our computational spatial analysis algorithm to calculate the G-score of baseline biopsy samples. G-score will be modeled as both a continuous variable and categorized into tertiles for analysis. G-scores will be correlated to patient characteristics, pathologic risk categories and pathologic response rates using Kruskal-Wallis and Wilcoxon rank-sum tests with a significance level of 0.05. Baseline G-scores categorized in tertiles will be correlated with survival outcomes using Kaplan Meier methods and compared with log rank tests with a significance level of 0.05.

15.3 Stopping Rule

In the event of excessive MK-3475-related toxicity leading to substantial delays in surgery (defined as more than 14 days' delay in 1 of the first 15 patients, 2 of the first 30 patients, 3 of the first 45 patients, or 5 of all patients enrolled) or in the event of excessive severe adverse events thought to be possibly, probably, or definitely related to study treatment (defined as grade 3-4 events occurring in 1 of the first 10 patients, 2 of the first 20 patients, 3 of the first 30 patients, 4

of the first 40 patients, 5 of the first 50 patients, or 7 of all patients enrolled) or in the event of any deaths on study thought to be possibly, probably, or definitely related to study treatment, the study will be stopped, AEs assessed, and the study will be considered for revision or closure.

16.0 INTERIM ANALYSIS

The goals of interim analysis of patients treated so far on this protocol are to (1) assess the clinical and pathologic responses in all patients who have received neoadjuvant pembrolizumab and (2) to assess correlative biomarkers including tumor cell PD-L1 staining and serum cytokine responses in relation to clinical and pathologic responses. To assess clinical and pathologic responses in these patients, we will compare clinical to pathologic staging in all patients who received the neoadjuvant dose comparing clinical staging established at initial diagnosis and assess any locoregional recurrence or distant metastases events in all 20 patients. Although, the 1-year post-treatment time point has been reached in about half the patients, we will describe the LRR/DM rates to current time points. For correlative studies, the pathology slides from the surgical resection will also be reviewed for immune infiltration and tumor cell status including in lymphadenectomy specimens. Tumor cell PD-L1 staining will be completed and analyzed on baseline and post-treatment specimens. We will assess exome and RNA-Seq data on a subset of the treated cohort that has completed data available at the McDonnell Genome Institute. Finally, multiplex serum cytokine assays will be completed to profile for any changes detectable in blood after neoadjuvant dosing.

16.1 Implication of Interim Analysis

Our primary motivation for performing the interim analysis is to assess whether the observed reduced rate of high-risk patients is related to the neoadjuvant dosing. Note that the retrospective analysis of the Washington University experience to identify the proportion of high risk patients in our population proposed in the previous amendment will complement the interim analysis of patients treated to date. Together, these data will show whether neoadjuvant pembrolizumab is downstaging patients (defined as a change in the clinical to pathologic stage) or is consistent with Washington University historical data.

Note that we are aware and have considered the implications of a downstaging effect of pembrolizumab. If we do find that neoadjuvant pembrolizumab is downstaging patients, we will submit a new amendment addressing this issue and how it may impact the study going forward.

17.0 RETROSPECTIVE REVIEW

The retrospective review of Washington University's experience with patients with clinically locally advanced oral cavity SCCs who have undergone surgery will be performed as follows:

Data from Washington University patients with clinically locally advanced oral cavity SCC who underwent surgery as initial therapy between 01/01/2010 and 12/31/2015 will be collected from an existing H&N registry titled "IMRT Treatment Outcome / Pattern of Failure Analysis" (HRPO# 201013031 / 04-0454). The following data points will be collected: name, date of birth, gender, oral cavity subsite, clinical T and N classification, pathologic T and N classification, ECE present/absent, margin positive/negative. Descriptive statistics will be used to describe patient and tumor characteristics.

These data will be compared to those from the prospective trial to test for differences in proportions between these two groups.

18.0 MULTICENTER REGULATORY REQUIREMENTS

Washington University requires that each participating site sends its informed consent document to be reviewed and approved by the Washington University Regulatory Coordinator (or designee) prior to IRB/IEC submission.

Site activation is defined as when the secondary site has received official written documentation from the coordinating center that the site has been approved to begin enrollment. At a minimum, each participating institution must have the following documents on file at Washington University prior to study activation:

- Documentation of IRB approval of the study in the form of a letter or other official document from the participating institution's IRB. This documentation must show which version of the protocol was approved by the IRB.
- Documentation of IRB approval of an informed consent form. The consent must include a statement that data will be shared with Washington University, including the Quality Assurance and Safety Monitoring Committee (QASMC), the DSMC (if applicable), and the Washington University study team.
- Documentation of FWA, signed FDA Form 1572 (if applicable), and the CVs of all participating investigators.
- Protocol signature page signed and dated by the investigator at each participating site.

The coordinating center Principal Investigator (or designee) is responsible for disseminating to the participating sites all study updates, amendments, reportable adverse events, etc. Protocol/consent modifications and IB updates will be forwarded electronically to the secondary sites within 4 weeks of obtaining Washington University IRB approval. Activated secondary sites are expected to submit protocol/consent/IB modifications to their local IRBs within 4 weeks of receipt unless otherwise noted. Upon the secondary sites obtaining local IRB approval, documentation of such shall be sent to the Washington University study team within 2 weeks of receipt of approval.

Documentation of participating sites' IRB approval of annual continuing reviews, protocol amendments or revisions, all SAE reports, and all protocol violations/deviations/exceptions must be kept on file at Washington University.

The investigator or a designee from each institution must participate in a regular conference call to update and inform regarding the progress of the trial.

19.0 REFERENCES

1. Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefebvre JL, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. The New England journal of medicine. 2004;350(19):1945-52.
2. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. The New England journal of medicine. 2004;350(19):1937-44.
3. Disis ML. Immune regulation of cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(29):4531-8.
4. Brown JA, Dorfman DM, Ma FR, Sullivan EL, Munoz O, Wood CR, et al. Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. Journal of immunology. 2003;170(3):1257-66.
5. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nature medicine. 2002;8(8):793-800.
6. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunological reviews. 2010;236:219-42.
7. Sharpe AH, Freeman GJ. The B7-CD28 superfamily. Nature reviews Immunology. 2002;2(2):116-26.
8. Thompson RH, Dong H, Lohse CM, Leibovich BC, Blute ML, Cheville JC, et al. PD-1 is expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. Clinical cancer research : an official journal of the American Association for Cancer Research. 2007;13(6):1757-61.
9. Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annual review of immunology. 2005;23:515-48.
10. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proceedings of the National Academy of Sciences of the United States of America. 2001;98(24):13866-71.
11. Zhang X, Schwartz JC, Guo X, Bhatia S, Cao E, Lorenz M, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity. 2004;20(3):337-47.
12. Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. Journal of immunology. 2004;173(2):945-54.
13. Riley JL. PD-1 signaling in primary T cells. Immunological reviews. 2009;229(1):114-25.
14. Sheppard KA, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS letters. 2004;574(1-3):37-41.
15. Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Molecular and cellular biology. 2005;25(21):9543-53.
16. Agata Y, Kawasaki A, Nishimura H, Ishida Y, Tsubata T, Yagita H, et al. Expression of the PD-1 antigen on the surface of stimulated mouse T and B lymphocytes. International immunology. 1996;8(5):765-72.

17. Vibhakar R, Juan G, Traganos F, Darzynkiewicz Z, Finger LR. Activation-induced expression of human programmed death-1 gene in T-lymphocytes. Experimental cell research. 1997;232(1):25-8.
18. Nishimura H, Honjo T, Minato N. Facilitation of beta selection and modification of positive selection in the thymus of PD-1-deficient mice. The Journal of experimental medicine. 2000;191(5):891-8.
19. Hamanishi J, Mandai M, Iwasaki M, Okazaki T, Tanaka Y, Yamaguchi K, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. Proceedings of the National Academy of Sciences of the United States of America. 2007;104(9):3360-5.
20. Uppaluri R, Dunn GP, Lewis JS, Jr. Focus on TILs: prognostic significance of tumor infiltrating lymphocytes in head and neck cancers. Cancer Immun. 2008;8:16.
21. Zandberg DP, Strome SE. The role of the PD-L1:PD-1 pathway in squamous cell carcinoma of the head and neck. Oral oncology. 2014;50(7):627-32.
22. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. The New England journal of medicine. 2012;366(26):2455-65.
23. Hodi FS, Dranoff G. The biologic importance of tumor-infiltrating lymphocytes. Journal of cutaneous pathology. 2010;37 Suppl 1:48-53.
24. Lemech C, Arkenau HT. Novel treatments for metastatic cutaneous melanoma and the management of emergent toxicities. Clinical Medicine Insights Oncology. 2012;6:53-66.
25. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nature reviews Cancer. 2012;12(4):252-64.
26. Phan GQ, Weber JS, Sondak VK. CTLA-4 blockade with monoclonal antibodies in patients with metastatic cancer: surgical issues. Annals of surgical oncology. 2008;15(11):3014-21.
27. Bristol-MeyersSquibb. YERVOY (ipilimumab): Serious and fatal immune-mediated adverse reactions—YERVOY Risk Evaluation and Mitigation Strategy (REMS). Available from: http://www.yervoy.com/hcp/rems.aspx.
28. Bristol-MeyersSquibb. YERVOY (ipilimumab) prescribing information revised March 2011. 2011.
29. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. The New England journal of medicine. 2012;366(26):2443-54.
30. Weber J, Thompson JA, Hamid O, Minor D, Amin A, Ron I, et al. A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma. Clinical cancer research : an official journal of the American Association for Cancer Research. 2009;15(17):5591-8.
31. Weber JS. Practical management of immune-related adverse events from immune checkpoint protein antibodies for the oncologist. American Society of Clinical Oncology educational book / ASCO American Society of Clinical Oncology Meeting. 2012:174-7.
32. Weber JS, Kahler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(21):2691-7.
33. JanssenBiotechIncorporated. REMICADE (Infliximab) prescribing information revised September 2011. 2011.
34. Deng H, Xiong S, Zhong R, et al. "Major pathologic response" in lymph nodes: a modified nodal classification for non-small cell lung cancer patients treated with neoadjuvant immunochemotherapy. *Exp Hematol Oncol.* 2023;12:40.

APPENDIX A: ECOG Performance Status Scale

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.