ClinicalTrials.gov ID: NCT02892201

Title: Pembrolizumab in HNSCC With Residual Disease After Radiation

Document Type: Protocol and SAP

Date: 5/7/2020

SPONSOR: Merck and Co, Inc.

TITLE: A Phase II study of Pembrolizumab for patients with head and neck squamous cell carcinoma with residual disease following definitive chemoradiation

VERSION: 6.1 (10.10.2018)

IND NUMBER: 131352

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APPROVED BY THE YALE UNIVERSITY IRB 5/7/2020

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1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab in HNSCC with residual disease after radiation
Trial Phase	*Phase II*
Clinical Indication	Patients with residual disease following definitive intent head and neck radiation with or without systemic therapy
Trial Type	This is a phase II study of pembrolizumab given at a constant dose of 200 mg every three weeks, for four cycles. Biopsy is repeated after four cycles. Patients with resectable disease can then go on to surgery, and patients with unresctable disease can continue on pembrolizumab until progression or for up to 1 year.
Type of control	none
Route of administration	IV
Trial Blinding	none
Treatment Groups	
Number of trial subjects	24
Estimated enrollment period	*18 months*
Estimated duration of trial	*18 months*
Duration of Participation	

2.0 TRIAL DESIGN

2.1 Trial Design

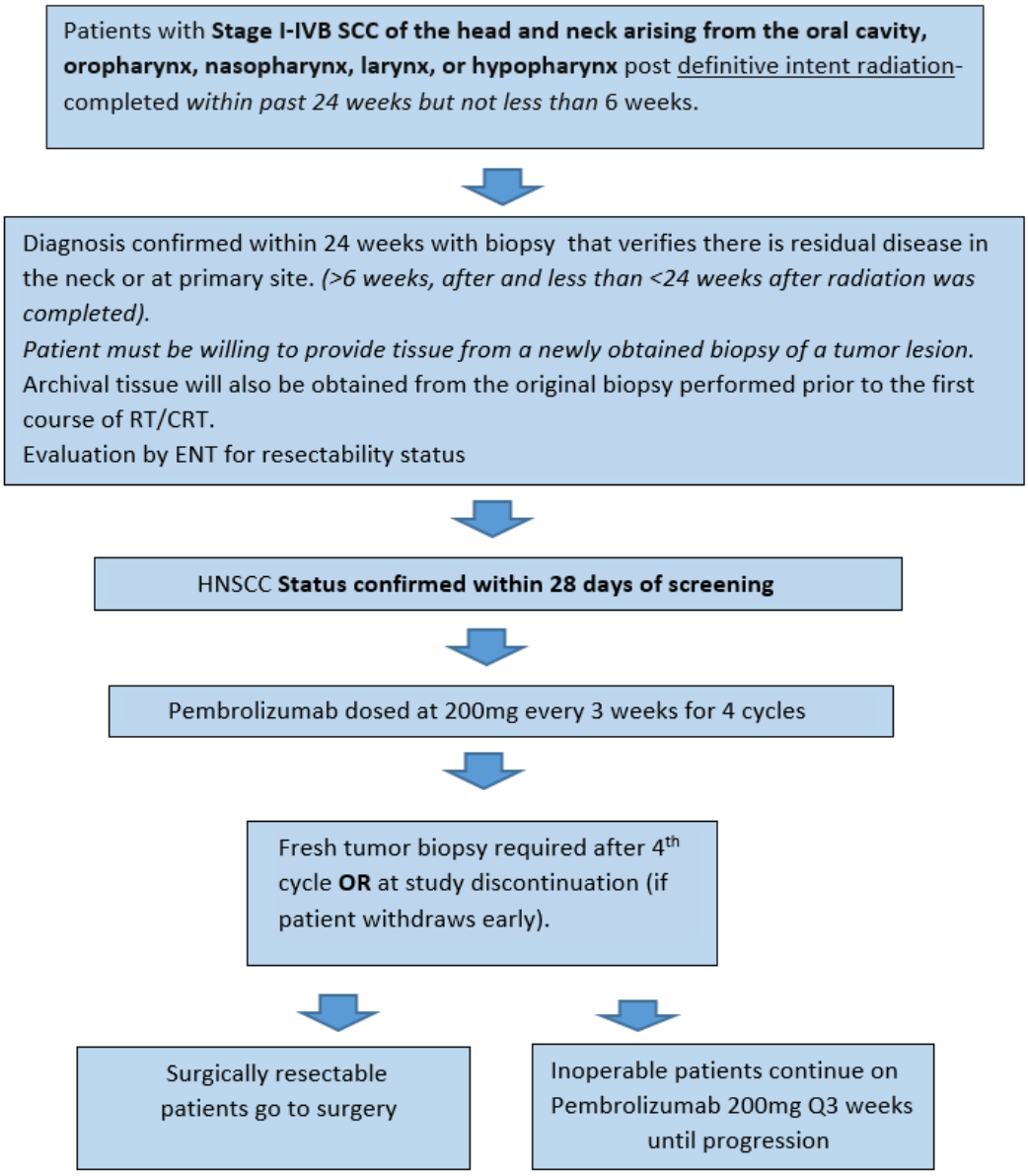
This is a phase II study for patients with squamous cell carcinoma of the head and neck who have residual disease following definitive therapy with radiation (with or without systemic therapy). Patients must be diagnosed with biopsy-proven residual disease within 24 weeks of completion of radiation therapy with or without systemic therapy. Residual disease must be biopsy proven and can be either from lymph nodes in the neck, or from the primary tumor site. Prior to beginning study therapy patients are evaluated by an ENT to determine if they have disease amenable to surgical resection. Both resectable and unresectable patients will be eligible for participation in the study. Patients will have repeat scans after 4 cycles (12 weeks) of treatment or disease progression, whichever comes first. Scans after 2 cycles will performed as clinically indicated.

Patients then receive four cycles of pembrolizumab at 200mg given every three weeks. Repeat imaging is performed after two cycles to ensure there is not progression of disease. Patients who were deemed resectable prior to being enrolled on the study who show clinical radiographic or clinical progression after two cycles of therapy will discontinue study drug and proceed to surgical resection. Patients deemed to have unresectable disease who have radiographic progression but have signs of clinical benefit can continue on the drug. Following completion of four cycles of therapy, a biopsy is performed, and patients are again evaluated by ENT surgery. Patients with disease considered amenable to surgery would go on to surgical

resection. Patients considered unresectable or who refuse surgery can continue pembrolizumab until time of progression or for 1 year.

The primary endpoint is the overall response rate. Secondary endpoints include change in PD-L1 expression from baseline, changes in key immune cells, and progression free survival.

2.2 Trial Diagram



3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** To determine the overall response rate to pembrolizumab for patients with residual disease following radiation with or without systemic therapy for squamous cell carcinoma of the head and neck. The response rate is defined at the time of progression or the completion of four cycles of therapy, whichever is earlier.

Hypothesis: The use of pembrolizumab in patients with residual disease following radiation with or without systemic therapy will lead to an enhanced overall response rate due to treatment-related priming of the immune response.

3.2 Secondary Objective(s) & Hypothesis(es)

1. To determine changes in PD-L1 expression following irradiation
    a. Hypothesis- irradiation will increase inflammation and PD-L1 expression

2. To determine the overall response rate as a function of PD-L1 expression
    a. Hypothesis- higher rates of PD-L1 expression will be associated with higher overall response rates

3. To evaluate median progression free survival and overall survival
    a. Hypothesis- based on limited data from previous studies the expected rate of DFS and OS are approximately 30% and 50% respectively

4. To determine the rate of immune related adverse events in patients receiving immunotherapy following radiation with or without systemic therapy
    a. Hypothesis- The rate of immune related events post radiation will be similar to that of the baseline rate receiving immunotherapy in the metastatic setting

5. To determine the rate of distant metastases
    a. Hypothesis- based on limited data from previous studies the expected rate of distant metastases is approximately 33%

3.3 Exploratory Objective

1. To determine the relative changes in levels of key immune cells including CD8+ T cells, CD4+ Tcells, Tregs, and FOXP3+ cells following radiation with or without systemic therapy and immunotherapy
2. To determine the baseline values and changes in PD-L1 expression in HPV(-) and HPV(+) tumors
3. To determine changes in PD-L1 expression in patients who received radiation alone, versus radiosensitizer based radiation
4. Rate of distant metastases

5. To examine PD-1/PD-L1 expression, tumor infiltrating lymphocytes, and other immune markers in responders to pembrolizumab, to define an immune signature predictive of post radiation response to the drug.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors . Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium,

whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

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

4.1.2 Preclinical and Clinical Trial Data

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

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Background

Head and neck squamous cell carcinoma (HNSCC) represents the 5th most common cancer worldwide. In the United States there are approximately 46,000 new diagnoses of head and neck squamous cell carcinoma and 8600 deaths from this cancer each year. Several randomized studies have established chemoradiation (CRT) as the definitive treatment approach for locally advanced head and neck squamous cell carcinomas (HNSCC)[1-5]. The CRT approach took hold largely because it became evident this approach could lead to organ and functional preservation[6]. While this was a major oncologic advance, it also presented a new problem, namely ensuring that patients had complete resolution of their disease in patients being treated with non-operative therapy. Early identification of patients that are non-responders or only partial responders to therapy is critical, as only a minority of patients who recur can receive curative intent salvage surgery[7].

Prolonged time to complete response to initial therapy

Unfortunately, clinical responses to therapy may be delayed. In the Princess Margaret Hospital experience of 493 patients undergoing definitive chemoradiation for head and neck SCC, approximately 50% had less than a complete response to chemoradiation therapy at 8-12 week post therapy assessment[8]. An additional 33% achieved CR between weeks 12 and 24. Of patients taken to neck dissection with less than a complete response (CR), the rate of positive residual tumor cells within the neck was 35%. This is substantially higher than the rate of positive residual cells at neck dissection in patients who achieve a CR to initial therapy, which

was 9%. Thus, it is estimated that approximately 10% of patients that would likely have had pathologic residual disease at the 8-12 week assessment will achieve pathologic CR by 24 weeks without any further intervention. This estimate is given by

the percentage of patients achieving a CR between weeks 12 and 24 x (the rate of pathologic

positivity in non-CR patients – the rate of pathologic positivity in CR patients)

= 33% x (35%- 9%) = 8.7%, or approximately 10%.

While the possibility of delayed complete response must be kept in mind, this is dwarfed by the proportion of patients with pathologic evidence of residual disease after completion of therapy, which in unselected analyses can be as high as 35%[8-12]. This number is expected to be higher in selected subgroups of patients with HPV(-) disease, locally advanced primary tumors (T3-T4), or advanced nodal disease (N2c-N3) [8, 13]

Outcomes in patients with residual disease

The presence of residual disease following definitive radiation/chemoradiation is an established prognostic marker for worsened disease specific survival in HNSCC patients[14]. In a 65 patient experience from Fox Chase Cancer Center, 43% of patients undergoing planned neck dissection for initial N2-N3 neck disease following chemoradiation were found to have persistent disease. This was associated with worsened locoregional control, recurrence free and overall survival[15]. The 3-year recurrence free survival rate in patients with positive residual neck disease was 37% in comparison to 85% in patients with no evidence of residual cells (p = 0.002). In a separate series of 35 patients with oropharyngeal carcinoma with clinical or radiographic evidence of residual neck disease, viable cancer cells were found in 68% of specimens. Of these, despite undergoing surgical resection of all known disease, 42% developed local recurrences, 29% developed regional recurrences and 25% failed distantly. Overall the 5-year disease specific survival was nearly 100% in patients without residual disease, but only 55% in patients with viable tumor cells[14]. A study from MSKCC looking at 56 patients who had neck dissections following chemoradiation demonstrated that 33% had viable tumor in their neck dissection specimens, and the 5-year overall survival (OS), disease specific survival (DSS), and relapse free survival (RFS) were worse in patients with viable tumor in their specimens (OS 49% vs. 93%, p = 0.0005; DSS 56% vs. 93%, p = 0.003; RFS 30% vs.75% p = 0.004)[16]. In patients with residual tumor cells, 63% developed recurrence, with 26% recurring locally, 19% recurring regionally, and 42% recurring distantly. Taken together, the results suggest that even in patients successfully salvaged with surgery, patients with viable tumor cells following radiation still have a worsened prognosis and are at high risk for local, regional, and distant failure suggesting alternative strategies for escalating therapy are needed.

Rationale for immunotherapy

Curative therapy for head and neck cancer has historically depended on surgery and/or radiation, and for patients with persistent or recurrent disease following initial curative therapy,

systemic therapy with DNA damaging agents, taxanes and EGFR inhibition, has had only a modest impact on survival. The identification of immune checkpoints as a potential target for anticancer therapy, with the possibility of sustained responses once T cell exhaustion is reversed, is thus of enormous interest in the field of head and neck cancer. As will be detailed below, the immune checkpoint ligand PD-L1 is expressed in head and neck cancer, and the PD-1 inhibitor pembrolizumab leads to monotherapy responses in both HPV-associated and HPV-negative head and neck cancer. The response rate initially reported in patients whose tumors express any PD-L1, defined as at least 1% of cells staining with a proprietary antibody to PD-L1, is approximately 20%; enrichment for patients with 50% or more of cells staining for PD-L1 is predictive of a higher response rate[17] (Jonathan Cheng, MD email communication, June 2014). Thus, strategies which induce inflammation with immune exhaustion, and which are associated with a higher degree of PD-L1 staining or greater tumor infiltration by lymphocytes, may be useful in increasing the proportion of patients who will be responsive to this promising class of agents. We propose evaluation of pembrolizumab in patients who have recently completed radiation with or without systemic therapy for locally advanced head and neck cancer as a population in whom tumor infiltration by lymphocytes and immune exhaustion with high expression of PD-L1 are likely to create a unique opportunity for enhanced response to immune checkpoint inhibition with pembrolizumab.

One novel strategy to deal with residual disease following RT/CRT is immunotherapy. Of particular interest is the PD-1/PD-L1 pathway, which is a negative regulator of immune response, and is the primary method of tumor immune evasion. PD-L1 is expressed on T-cells, B-cells, macrophages, dendritic cells and solid tumors, and is inducible by cytokines. PD-L1 activates PD-1 on T-cells, which down regulates T-cell effector function allowing cancer cells to evade immune surveillance.

PD1/PDL-1 in head and neck cancer

PD-L1 expression in human HNSCC tissue samples is reported in 46.4-100% of cases, although the definition of staining necessary to be considered positive varies from study to study. Ranges of PD-L1 expression are 49.2-70% in HPV (+) tumors and 29-40% in HPV (-) tumors, with a trend towards increased expression in HPV (+) tumors[18]. That targeting this pathway is of clinical benefit was demonstrated in a phase 1B study of pembrolizumab, an anti-PD-1 antibody. In patients with recurrent or metastatic HNSCC, pembrolizumab demonstrated a 20% response rate in heavily pretreated patients[17]. Depending on the level of PD-L1 expression chosen as a cutoff, however, the response rate could be as high as 45.5%.

Given that the response to anti PD-1 therapy appears related to levels of PD-L1 expression, and the fact that PD-L1 is inducible, the potential impact of radiation therapy on PD-L1 expression is of considerable interest. A study of TUBO tumors treated with 12 Gy of radiation and examined three days later demonstrated an increase in expression of PD-L1 on dendritic cells and tumor cells, compared with controls[19]. This is in keeping with other well-documented effects of radiation on the immune system. Radiation leads to enhanced T-cell infiltration in the tumor microenvironment, promotes T-cell cytokine production and cytotoxicity, and increases the expression of tumor antigens, thereby improving tumor cell antigenicity[20].

Also enticing is the potential for a synergistic effect between immunotherapy and radiation. In a preclinical mouse glioma cell line, the combination of radiation therapy and PD-L1 blockade led to a near doubling of survival in comparison to either a PD-L1 alone arm, or a radiation alone arm[21]. In addition, the combined treatment group demonstrated an increase in CD8 effector T-cells (CD8/IFN- γ/TNF- α) and a decreased number of regulatory T-cells (Tregs, CD4/FOXP3+) compared to controls. Moreover, to test for long-term immunity, untreated, and "cured" mice were challenged with flank injection of GL261-luc tumor cells. All naïve mice developed tumors by 21 days after injection, whereas none of the "cure" mice developed tumors within 60 days of implantation, suggesting this approach leads to prolonged protective T-cell immunity.

Given the poor outcomes of patients with residual disease following CRT, the high levels of PD-L1 expression in HNSCC, the evidence of clinical response to PD-1 inhibitors in metastatic and recurrent HNSCC, and the upregulation of PD-L1 following irradiation in mice, the use of CRT as a potential priming agent for immunotherapy is promising. Thus, the purpose of this study is to determine whether radiation with or without systemic therapy can upregulate PD-L1 expression, thus optimizing patients with residual disease for anti-PD-1 therapy.

4.2.2 Rationale for Dose Selection/Regimen/Modification

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

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

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to

remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

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

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

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

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The proposed strategy of pembrolizumab in this poor prognosis group of patients with residual disease will be deemed a strategy worthy of further investigation if the overall response rate could be increased to 27%.

4.2.3.2 Biomarker Research

The phase I dose escalation study of pembrolizumab in patients with metastatic and previously treated HNSCC demonstrated that response was noted in 20% of patients overall, although in patients with higher levels of PD-L1 expression, this number could be as high as 45.5%[17]. Overall the percentage staining positive for PD-L1 for HNSCC as a group was 78%. The expression of PD-L1 has also been correlated with the extent of tumor lymphocytic infiltrate. The latter has been observed to be increased after radiation therapy, suggesting one possible mechanism for an improved systemic response after radiation. We propose here to treat HNSCC patients without regard to PD-L1 expression on biopsies done just prior to initiation

of pembrolizumab. Tissue specimens will be obtained after pembrolizumab treatment and local response will be correlated to expression.

Studies conducted by Dr. Lieping Chen's group, that characterized the PD-L1/PD-1 axis a number of years ago, suggest that presence of CD4 and CD8 positive cells in tumor deposits is important for response to PD-1 targeting therapies[22]. These investigators found that the majority of PD-L1 positive tumors were associated with CD4 and CD8 tumor infiltrating lymphocytes (TILs), while the minority of the PD-L1 negative tumors had associated TILs.

Studies have demonstrated that 33-47% of HSNCC show a T-cell inflamed phenotype (TCIP) similar to melanoma, and this phenotype may in turn identify a subgroup particularly sensitive to immunotherapy[23]. Moreover, a strong correlation exists between the T-cell inflamed phenotype and the mesenchymal intrinsic subtype of HNSCC in both HPV(+) and HPV (-) disease, which has been shown to be associated with improved overall survival[24].

An additional potential biomarker of tumor response is cell-free tumor-derived circulating DNA (ctDNA). The laboratory of Abhi Patel has developed an ultrasensitive assay for measuring small amounts of cell-free mutant DNA released into the blood from dying tumor cells[25]. The assay covers a broad panel of mutations and uses novel error suppression techniques applied to next-generation sequencing data to enable identification of rare mutant DNA down to a fractional abundance of ~0.02%. Because such ctDNA is highly tumor-specific and is rapidly cleared from the bloodstream, it is showing excellent promise as a quantitative cancer biomarker. Indeed, we (and others) have observed decreases in ctDNA levels following treatment with surgery, radiation therapy, and systemic therapy (sometimes with an initial spike from tumor kill). Thus, we hypothesize that quantitative changes in ctDNA may provide information that is complementary to radiologic studies for tracking the efficacy of treatment with the PD-1 inhibitor pembrolizumab in patients with HNSCC.

5.0 METHODOLOGY

5.1.1 Subject Inclusion Criteria

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

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

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

3. Have biopsy-proven residual disease. Measurable disease per RECIST 1.1 is not required. All measurements should be recorded in order to evaluate response..

4. Be willing to provide tissue from a newly obtained core biopsy of a tumor lesion. *Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1 and following completion of RT/CRT. Tissue from fine needle aspirations (FNA) may be used if sufficient tissue is available.*

5. Have a performance status of 0 or 1 or 2 on the ECOG Performance Scale.

6. Demonstrate adequate organ function as defined in Table 1 Labs value need to be assessed within 14 days of study treatment.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
Albumin	≥2.5 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

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

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

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

10. Patients must have a history of Stage I-IVB SCC of the head and neck arising from the oral cavity, oropharynx, nasopharynx, larynx, or hypopharynx and must have been treated with definitive intent radiation (with or without systemic therapy)

11. Patients must be at least 6 weeks (42 days) and no more than 24 weeks (168 days) from completion of radiation with or without systemic therapy at the time of the biopsy confirming residual disease. Patients must receive the first dose of study medication no more than 28 weeks following completion of radiation.

12. Patients must have pathological evidence of persistent lymph node disease or persistent disease at the primary tumor site with viable tumor cells confirmed by a biopsy within 24 weeks of study treatment and no evidence of metastatic disease following primary radiation with or without systemic therapy confirmed by a CT scan within 4 weeks of study treatment. If a biopsy confirming residual disease has not been performed, this can be performed after obtaining consent, during the screening procedures.

13. Persistent lymph node disease with viable tumor cells will be determined by the histological determination of tumor viability.

14. All persistent disease must have received at least 66 Gy in 1.8-2Gy fractions of radiotherapy to the area of residual disease (or a biologically equivalent dose given by the linear quadratic equation: biologically equivalent dose (BED) = nd (1 + d/(**α/β), where n is** the number of fractions, **d** dose per fraction and the **α/β** ratio for tumor is 10. Previous radiation records will be obtained to confirm adequate dosing.

5.1.2 Subject Exclusion Criteria

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

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

2. Has a diagnosis of immunodeficiency or is receiving supraphysiologic doses of systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. A physiologic dose of steroids is defined as up to 10mg of prednisone daily (or its equivalent).

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

4. Hypersensitivity to pembrolizumab or any of its excipients.

5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from acute, non-hematological adverse events due to agents administered more than 4 weeks earlier unless otherwise approved by the Principal Investigator.

    - Note: Subjects with ≤ Grade 2 neuropathy, any grade dysphagia, ≤ Grade 2 pain, ≤ Grade 2 weight loss, any grade hyperpigmentation of skin, any grade fatigue, any grade xerostomia, and any grade dysgeusia, are an exception to this

criterion and may qualify for the study. Also please note that the presence of a feeding tube to aid with nutrition does not disqualify patients from study.

- Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

6. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to the first protocol treatment or who has not recovered (i.e., ≤ Grade 1 or at baseline) from acute, non-hematological adverse events due to a previously administered agent unless otherwise approved by the Principal Investigator.

    - Note: Subjects with ≤ Grade 2 neuropathy, any grade dysphagia, ≤ Grade 2 pain, ≤ Grade 2 weight loss, any grade hyperpigmentation of skin, any grade fatigue, any grade xerostomia, and any grade dysgeusia, are an exception to this criterion and may qualify for the study. Also please note that the presence of a feeding tube to aid with nutrition does not disqualify patients from study.

    - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

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

8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

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

10. Has known history of non-infectious pneumonitis that required steroids, or current pneumonitis.

11. Has an active infection requiring systemic therapy.

12. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for

the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

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

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

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

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

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

18. Has received a live vaccine within 30 days of the first protocol treatment.

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

19. Any patient receiving adjuvant systemic therapy following the completion of radiation therapy is ineligible.

20. Any patient with evidence of distant metastatic disease on a CT within 4 weeks of treatment is ineligible.

21. Evidence of interstitial lung disease.

5.2 Trial Treatments

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

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

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

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

5.2.1.2 Dose Modification

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

Table 3

Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism	2-4	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.
[1] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.
[2] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record. Dosing may be interrupted for up to 6 weeks at the end of cycle 4 as protocol required assessments to determine treatment continuation are performed.

5.2.2 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

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

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

5.2.3 Trial Blinding/Masking

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

5.3 Treatment Allocation

Patients with Stage I-IVB HNSCC of the larynx, hypopharynx, oropharynx, nasopharynx, or oral cavity) who have been treated with curative intent radiation, chemoradiation, or cetuximab and radiation within 6-24 weeks and have biopsy proven residual disease will be eligible for enrollment.

All patients upon biopsy confirmation of residual disease will have restaging scans (CT neck/chest/abdomen/pelvis). Patients will require evaluation by an ENT to determine whether their disease is considered resectable or unresectable. Patients will then receive pembrolizumab at a dose of 200mg Q3 weeks for 4 cycles. A CT scan of the neck/chest/abdomen/pelvis will be performed at the end of cycle 2 to check for progression of disease (irPD), defined using immune related response criteria. Patients with progression prior to four cycles of pembrolizumab will discontinue study therapy.

After four cycles patients will undergo repeat CT neck/chest/abdomen/pelvis and a biopsy. Patients will then be re-evaluated by otolaryngology to determine the current status of their local/locoregional disease and to determine whether it is technically resectable. At this time patients that are deemed resectable can go on to surgical resection, and those deemed unresectable or who refuse resection can continue on pembrolizumab until evidence of progression or for up to 1 year. These patients will not be evaluable for the study endpoints, although their response rates and overall survival will be reported. An early stopping rule exists, such that during enrollment of the first 10 patients considered resectable, at screening if 3 or more become unresectable during the study the trial will close. The plan is to enroll 24 patients.

5.4 Stratification

Since this is a single arm Phase II study, enrollment will not be stratified.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

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

5.5.1 Acceptable Concomitant Medications

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

and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 6.3.

5.5.2 Prohibited Concomitant Medications

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

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

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

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these

measures may include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance detailed in Section 6.3.3.2, but does not need to follow the treatment guidance. Refer to Section 5.2.1 for dose modification.

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

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

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

    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
    - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
    - For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

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

    - For **T1DM** or **Grade 3-4** Hyperglycemia

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

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

- **Hyperthyroidism or Hypothyroidism**:
  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

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

- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with oral corticosteroids.

- For **Grade 3-4** events, treat with systemic (intravenous) corticosteroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

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

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

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (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

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 6.3.2-Reporting of Pregnancy and Lactation to the Sponsor and to Merck. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours to the Sponsor and within 2 working days to Merck if the

outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 6.3.2.

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 6– Other Procedures.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator’s decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 12 months of uninterrupted treatment with pembrolizumab or 17 administrations of study medication, whichever is later.
- *Note: 12 months of study medication is calculated from the date of first dose.* Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section .6.2.5 (Visit Requirements).

From the administration of first treatment until 30 days (unless otherwise specified) subsequent to last treatment or withdrawal of subject, new onset adverse events will be captured. Follow-up and reporting of these events will follow the same procedure as for AEs observed during the study period. Serious Adverse Events will be collected for 90 days after the end of treatment as described in Section 6.3. In addition, any unexpected SAE that occurs more than 90 days after drug administration but is possibly, probably or definitely attributed to drug administration will be recorded and reported.

Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8.1 Discontinuation of Study Therapy after CR

Among patients who are not at the conclusion of 4 cycles of pembrolizumab candidates for surgery, or for those who refuse surgery at that time point, pembrolizumab will be continued for one year. Discontinuation of pembrolizumab in this cohort may be considered for subjects who subsequently attain a confirmed CR and have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared.

5.9 Subject Replacement Strategy

Patients will be replaced if they do not receive at least one cycle of pembrolizumab.

5.10 Clinical Criteria for Early Trial Termination

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

1. Quality or quantity of data recording is inaccurate or incomplete

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

4. Plans to modify or discontinue the development of the study drug

5. An early stopping rule will be put into place such that if at any time during enrollment of the first 10 patients considered initially resectable at screening, if 3 or more of these patients have local progression on the study treatment and are then deemed locally unresectable the trial will close early.

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

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	**Screening Phase**	**Study Treatment Cycles**					**Continuation Treatment Cycles**				**End of Treatment**		**Post-Treatment**	
							To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Main Study Screening (Visit 1)	1	2	3	4	4D21	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	±7	± 3	± 3	± 3	± 3	At time of Discon ± 3	30 days post discon[1] ± 7	Every 8 weeks post discon ± 7	Every 12 weeks ± 7
	Administrative Procedures													
Informed Consent	X													
Inclusion/Exclusion Criteria	X													
Demographics and Medical History	X													
Prior and Concomitant Medication Review	X	X	X	X	X		X	X	X	X	X			
Pembrolizumab Administration		X	X	X	X		X	X	X	X				
Post-study anticancer therapy status													X	X
Survival Status														X
ENT evaluation for resectability status	X					X[14]					X[14]			
	Clinical Procedures/Assessments													
Review Adverse Events		X	X	X	X		X	X	X	X	X	X[1]	X[13]	X[13]
Full Physical Examination	X													
Directed Physical Examination		X	X	X	X		X	X	X	X	X		X	
Vital Signs and Weight[2]	X	X[3]	X[3]	X[3]	X[3]		X[3]	X[3]	X[3]	X[3]	X		X	
ECOG Performance Status	X	X[4]	X[4]	X[4]	X[4]		X[4]	X[4]	X[4]	X[4]	X		X	
	Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory													
Pregnancy Test – Urine or Serum β-HCG	X													
PT/INR and aPTT	X[5]													
CBC with Differential	X[5]	X	X[6]	X[6]	X[6]		X[6]	X[6]	X[6]	X[6]	X			
Comprehensive Serum Chemistry Panel, Magnesium, Phosphorous, LDH, LFTs	X[5]	X	X[6]	X[6]	X[6]		X[6]	X[6]	X[6]	X[6]	X			
Urinalysis	X[5]		X[6]		X[6]			X[6]		X[6]				
T3, FT4 and TSH	X[5]		X[6]		X[6]			X[6]		X[6]				

Trial Period:	**Screening Phase**	**Study Treatment Cycles**					**Continuation Treatment Cycles**				**End of Treatment**		**Post-Treatment**	
							To be repeated beyond 8 cycles							
Treatment Cycle/Title:	Main Study Screening (Visit 1)	1	2	3	4	4D21	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	±7	± 3	± 3	± 3	± 3	At time of Discon ± 3	30 days post discon[1] ± 7	Every 8 weeks post discon ± 7	Every 12 weeks ± 7
	Efficacy Measurement													
CT neck/chest/abdomen/pelvis	X[7]		X[11]		X[11]			X[11]		X[11]			X[12]	
	Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood													
Archival Tissue Collection	X[8]													
Newly Obtained Tissue Collection	X[9]					X[10]					X[10]			
Correlative Studies Blood Collection	X					X					X[15]			

1. In the case that a patient initiates a subsequent anti-cancer therapy the 30 day follow up should occur prior to the first dose of the new therapy and patients will move to survival follow up.
2. Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.
3. Vital signs will be taken prior to the administration of each dose of trial treatment and at discontinuation of each treatment.
4. ECOG status will be evaluated prior to the administration of each dose of trial treatment and at discontinuation of each treatment.
5. Screening lab will be assessed within 14 days of first treatment.
6. After cycle 1, pre-treatment labs can be drawn up to 72 hours pre-dose.
7. The baseline CT scan can be from before study enrollment as long as the scan is within 4 weeks of study treatment.
8. Archival tissue from a biopsy prior to radiation treatment with or without systemic therapy should be requested.
9. All patients will have a biopsy prior to the start of study treatment. This specimen may be obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1 and following completion of RT/CRT. This pre-treatment biopsy can be used to confirm residual disease.
10. Patients will have a research biopsy after completion of the 4th treatment cycle or at study discontinuation if they come off treatment before cycle 4. There will be no additional biopsy for patients who stay on treatment past 4 cycles.
11. Imaging during study treatment cycles will occur at the end of cycle 2 when clinically indicated and cycle 4 or at disease progression whichever comes first (required). Less frequent imaging is acceptable during the continuation cycles, although a minimum of every 8 weeks is recommended.
12. If a patient comes off trial for reasons other than disease progression imaging should be done every 9 weeks ±7 days
13. Information on SAEs will be collected for 90 days after the end of treatment. Any unexpected SAE that occurs more than 90 days after drug administration but is possibly, probably or definitely attributed to drug administration will be recorded and reported.
14. Patients will have a repeat ENT evaluation for resectability status after completion of the 4th treatment cycle or at study discontinuation if they come off treatment before cycle 4. There will be no additional ENT evaluation for patients who stay on treatment past 4 cycles
15. Correlative blood collection will occur at end of cycle 4 as well as at discontinuation, unless discontinuation within past 21 days.

6.2 Trial Procedures

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

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

6.2.1 Patient Registration Process

Prior to obtaining signed consent from a patient, the site principal investigator or coordinator must email the project manager to inquire about study space availability. If a slot is available, the Project Manager will provide a study ID and the potential study participant will complete the consent process. The informed consent process must be completed before any study screening procedures may begin. Following consent, patients will have all required screening procedures outlined in Section 6. The site principal investigator or other approved investigator must document that the patient has met all inclusion criteria and has none of the exclusion criteria. Following completion of eligibility testing, eligibility documents will be sent to the project manager. Examples of required documents are listed in the manual of operations.

Upon review and approval of the Project Manager an email will be sent s to the site with confirmation of eligibility.

6.2.2 Administrative Procedures

6.2.2.1 Informed Consent

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

6.2.2.2 General Informed Consent

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

A copy of the signed and dated consent form should be given to the subject before participation in the trial. The consent process must be documented and available for review in the patients research chart.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable

representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. This can occur via written documentation (a formal letter), in person conversation or a phone call prior to an amended consent document becoming available. Regardless of the method the procedure must be documented and kept in the research file. As soon as possible this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

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

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

6.2.2.3 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the local investigator. All patients will be registered to this trial locally by the project manager. See Patient Registration (section 6.2.1) for more information.

6.2.2.4 Medical History

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

6.2.2.5 Prior and Concomitant Medications Review

6.2.2.5.1 Prior Medications

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

6.2.2.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 6.3.

6.2.2.6 Disease Details and Treatments

6.2.2.6.1 Disease Details

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

6.2.2.6.2 Prior Treatment Details

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

6.2.2.6.3 Subsequent Anti-Cancer Therapy Status

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

6.2.2.7 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 10.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs).

Please refer to section 6.3 for detailed information regarding the assessment and recording of AEs.

6.2.2.8 Full Physical Exam

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

6.2.2.9 Directed Physical Exam

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

6.2.2.10 Vital Signs

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

6.2.2.11 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 10.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

6.2.2.12 Tumor Imaging and Assessment of Disease

CT neck, chest, abdomen and pelvis will be ordered at baseline and during the 3rd week of cycles 2, if clinically indicated,cycle 4 or at time of progression whichever comes first. Additional re-imaging may be obtained at the discretion of the investigator. For patients who are not amenable to resection following 4 cycles of therapy and who continue on pembrolizumab, a q8 week CT of the neck, chest, abdomen and pelvis will be obtained.

6.2.2.12.1 Measurement of Response

Following pembrolizumab, response will be measured in comparison to the most immediate pre-pembrolizumab imaging study. For complete definitions of measurable and non-measurable disease, please refer to the RECIST v1.1 criteria.

1. For lesions that meet the criteria for measureable disease outlined in RECIST 1.1, the standard RECIST response criteria will apply

RECIST response criteria:

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

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

Progressive disease:At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also

demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable disease: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2. The following 2 criteria for evaluation of clinical response will apply for l**esions considered too small for measurement by RECIST 1.1** (for example nodes with short axis < 1.5cm or primary lesions or skin lesions < 1cm).

The lesion would have to shrink to < 1cm in all three dimensions and also have at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

AND

One of the following two criteria are true:

1) Either the biopsy performed after pembrolizumab shows no active cancer

   OR

2) The patient has a PET scan after pembrolizumab which demonstrates that a previously active lesion (SUV >/= 3.0 is now PET negative (SUV < 3.0)).

In the case where both PET and biopsy are both performed, and the results are disparate, the biopsy results will take precedence. For example a positive biopsy in this situation would connote a designation of response as a PR, and a negative biopsy would connote a response as a CR.

Response will be evaluated by imaging studies as described in the study calendar. If symptoms develop or clinical deterioration occurs, patients may be imaged prior to the pre-specified time points for imaging.

6.2.2.12.2 Evaluation of Best Overall Response

The Best Overall Response is the best response recorded from the start of the treatment until completion of four cycles of study drug (taking as reference for progressive disease the smallest measurements recorded since the treatment started). For purpose of the primary endpoint of the study, the overall response will be measured during the post pembrolizumab, in comparison to the most immediate pre-pembrolizumab imaging.

6.2.2.12.3 Progression-Free and Overall Survival

For the purpose of the secondary endpoints of this study, PFS is defined as the time from initiation of study drug until the first documented, confirmed progression of disease. PFS will

also be measured and reported from the initiation of study drug. OS will be measure from the initiation of study therapy.

6.2.2.13 Tumor Tissue Collection and Correlative Studies Blood Sampling

Before and during trial therapy, if a lesion is biopsied or for clinical purposes, a sample will be retained for protocol-related correlative studies. If a patient has had a previous biopsy, the pre-treatment sample may be taken from paraffin-embedded tissue.

6.2.2.13.1 Study-Related Biopsies and Tissue Collection

Tissue from fresh tissue (see below) is required at study entry. Fresh tumor biopsy is required one time after pembrolizumab. These requirements may be waived by the principal investigator.

Tumor tissue will be obtained prior to initiation of study therapy from any primary or locoregional disease site and processed according to the specifications of the lab manual. When a biopsy is being done for standard-of-care clinical purpose, tissue will be obtained from this procedure if available. Otherwise a study-related biopsy will be done.

If the patient undergoes a biopsy at any point during protocol therapy for clinical purpose, extra tumor tissue will be collected for study purposes if available.

6.2.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5.

Table 5 Laboratory Tests

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

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

‡ If considered standard of care in your region.

After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

6.2.3.1 Blood Collection for Serum Pembrolizumab

Sample collection, storage and shipment instructions for serum samples will be provided in the Laboratory Manual.

6.2.3.2 Blood Collection for Anti-Pembrolizumab Antibodies

Sample collection, storage and shipment instructions for blood samples will be provided in the Laboratory Manual.

6.2.4 Other Procedures

6.2.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 6.3 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 12 months of treatment with pembrolizumab may discontinue treatment After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 6.2.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 6.2.5.3.2).

6.2.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 6.2 - Trial Procedures.

6.2.5.1 Screening Period

Prior to initiation of study therapy, the patient will require a screening visit. Scans, and evaluations should be done as close to the initiation of therapy as feasible, and no more than 28 days prior. Laboratory studies should be completed within 14 days of initiation of therapy. In some cases labs will need to be repeated if screening lasts longer than 14 days. The following should be addressed at the screening visit:

1. Informed Consent
2. Medical History
3. Complete physical examination, vital signs, and measurement of height and weight
4. Review of prior and concomitant medications
5. CT scan of chest, abdomen and pelvis

6. ECOG Performance status evaluation
7. Determination of baseline adverse event status
8. Pregnancy test for women of childbearing potential, and counseling that sexually active women of childbearing potential must use an effective form of birth control during the entire study period
9. Determination of sufficient tumor specimen for evaluation of PD-L1 status
10. Laboratory studies: CBC with differential, serum chemistries, liver function tests, LDH, TSH, T3 and Free T4, PT/INR and PTT, uranalysis
11. Collection of blood, fresh (within 6 weeks) tissue and archival tissue for correlative studies
12. Evaluation by an ENT

6.2.5.2 Treatment Period

On-study visits will occur on day 1 of each cycle of MK-3475, and will include the following at every visit:

1. Directed physical examination, vital signs, and measurement of weight
2. Review of concomitant medications
3. Performance status evaluation
4. Determination adverse events
5. Laboratory studies: CBC with differential, serum chemistries, liver function tests, LDH
6. TSH and Free T4 will be done every other cycle starting with Cycle 2
7. CT scans of chest, abdomen and pelvis will be done at the end of cycles 2 if clinically indicated and end of cycle 4.
8. Collection of blood at the end of cycle 4 for correlative studies. Collection of and fresh tissue at the end of cycle 4 or at discontinuation if earlier
9. Evaluation by an ENT at the end of cycle 4 or at discontinuation if earlier

After clinically evident progression or if the patient is discontinuing treatment for any reason the patient will be seen for a study visit, at which the following will be addressed:

1. Directed physical examination, vital signs, and measurement of weight
2. Review of concomitant medications
3. Performance status evaluation
4. Determination adverse events
5. Collection of blood for correlative studies, unless end of cycle 4 collection within 21 days. Collection of fresh tissue for correlative studies if not already taken at end of cycle 4 as described above.
6. Evaluation by an ENT
7. CT scans of chest, abdomen and pelvis if not already taken at end of cycle 4

Fresh tumor specimens will be obtained if feasible during therapy if the patient undergoes resection or biopsy for a standard-of-care clinical purpose per the study flow chart.

6.2.5.3 Post-Treatment Visits

6.2.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Any unexpected SAE that occurs more than 90 days after drug administration but is possibly, probably or definitely attributed to drug administration will be recorded and reported.

6.2.5.3.2 Follow-up Visits

At each follow up visit patients will have a directed physical exam, including ECOG performance status, vital signs and weight. A comment will also be made regarding the post-study anticancer status. Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 8 weeks (± 7 days) with imaging done every 9 weeks (± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, or end of the study Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

6.2.5.3.3 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone

every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.3 Assessing and Recording Adverse Events

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

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

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

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

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

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination. Adverse events will be recorded on an Adverse Event log and entered in OnCore within 72 hours of the site becoming aware of the event.. The reporting timeframe for adverse events meeting any serious criteria is described in section 6.3.3.1.

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

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

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the project manager. The project manager will report all overdoses within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220). Sites are responsible for reporting to their IRB per local policy.

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

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

Such events must be reported within 24 hours to the project manager. The project manager will report these events within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220). Sites are responsible for reporting to their IRB per local policy.

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

6.3.3.1 Serious Adverse Events

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

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

- Is an other important medical event

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

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, and any unexpected Serious Adverse Event that occurs more than 90 days after drug administration but is possibly, probably or definitely attributed to drug administration, must be reported within 24 hours to the Yale project manager and protocol PI. The Yale project manager will report within 2 working days to Merck Global Safety. Sites are responsible for reporting to their IRB per local policy.

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

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Yale project manager who will then report to Merck. .All SAEs should be entered into OnCore within 24 hours of the site becoming aware of the event.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220

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

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

6.3.3.2 Events of Clinical Interest

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

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 6.3.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

ECIs (both non-serious and serious adverse events) identified above from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220), regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

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

6.3.4 Evaluating Adverse Events

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

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

Table 6 Evaluating Adverse Events

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

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

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

6.3.5 Sponsor Responsibility for Reporting Adverse Events

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

7.0 STATISTICAL ANALYSIS PLAN

7.1 Statistical Analysis Plan Summary

The primary objective of this phase II study is to determine the overall response rate in patients with squamous cell carcinoma of the head and neck who have residual disease following definitive radiation with or without systemic therapy. This will be a single arm study of 24 patients with Stage I-IVB HNSCC who have residual disease after being treated with definitive radiation with or without systemic therapy.

The expected rate of resolution of disease without any further therapy is thought to be approximately 10%. This is derived from the Princess Margaret Hospital experience of 493 patients undergoing definitive chemoradiation for head and neck SCC, approximately 50% had less than a complete response to chemoradiation therapy at 8-12 week post therapy assessment[26]. An additional 33% achieved CR between weeks 12 and 24. Of patients taken to neck dissection with less than a complete response (CR) the rate of positive residual tumor cells within the neck was 35%. This is substantially higher than the rate of positive residual cells at neck dissection in patients who achieve a CR to initial therapy, which was 9%. Thus it is estimated, that approximately 10% of patients that would likely have had pathologic residual disease at the 8-12 week assessment will achieve pathologic CR by 24 weeks without any further intervention. This estimate is given by:

the percentage of patients achieving a CR between weeks 12 and 24 x (the rate of pathologic positivity in non CR patients – the rate of pathologic positivity in CR patients)

= 33% x (35%- 9%) = 8.7%, or approximately 10%.

Thus, assuming a baseline response rate of 10% (based on the Princess Margaret experience discussed above) and an improvement in response rate to 27% after treatment of chemoradiation, we will have 81% power to detect this difference with 24 patients by exact one-sample binomial test at one-sided significance level of 0.10. If 27% or more of patients in the study develop a partial or complete response to pembrolizumab, this strategy will be deemed worth of further investigation.

The primary endpoint of this trial will be overall response rate and the secondary endpoint will be progression-free survival. We will use descriptive statistics to calculate frequency and proportion for the response rate to pembrolizumab. 95% confidence interval will also be provided. Exact binomial test will be used to compare the observed response rate versus historical control. For the secondary endpoint, we will use Kaplan-Meier estimator to present the progression-free survival.

8.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

8.1 Investigational Product

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

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

Table 7 Product Descriptions

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

8.2 Packaging and Labeling Information

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

8.3 Clinical Supplies Disclosure

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

8.4 Storage and Handling Requirements

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

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

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

8.5 Returns and Reconciliation

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

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

9.0 ADMINISTRATIVE AND REGULATORY DETAILS

9.1 Compliance with Trial Registration and Results Posting Requirements

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

9.2 Quality Management System

9.2.1 Safety Monitoring

The Yale Cancer Center Data and Safety Monitoring Committee (DSMC) will provide the primary oversight of data and safety monitoring. The Yale DSMC will review and monitor compliance, toxicity and deviations from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator.

The DSMC will review this protocol at a minimum of once every six months. Information to be provided to the committee includes: a study narrative by the PI, a summary DSMC report produced by OnCore (which includes participant accrual, response, trial status history, SAEs, Adverse Events, Deviations and survival); audit results, and monitoring reports as applicable. Other information (e.g. scans, laboratory values) will be provided upon request.

9.2.2 Data Monitoring

The study principal investigator and YCCI are responsible for monitoring the performance of all of the participating sites. This will be performed by conducting a study site initiation visit, as well as regularly scheduled monitoring visits and/or remote monitoring throughout the life of the protocol. At the end of the trial, the monitor will then perform a study site close-out visit at all participating sites.

YCCI will utilize their institution's initiation, monitoring and close-out visit reports. Following each site visit, a visit report will be generated containing information on site activities, and a summary of pertinent points and action items together with a copy of the follow-up letter will be sent to each investigative site.

During these monitoring visits, some of the items that will be reviewed are the following:

- Training of the sites
- Site personnel qualifications to participate in the trial
- That study related documents are current
- That regulatory compliance is accomplished
- That each subject has signed the informed consent
- That the current and approved protocol is complied with (including reporting and logging of all protocol deviations)
- That all SAEs and AEs have been reported to the local regulatory and Ethics/IRB Committees, YCCI and Merck, as appropriate
- That source documentation matches CRFs
- That required procedures for study drug accountability, distribution, and storage are followed.

YCCI will document the required study monitoring activities in a Study Monitoring Plan.

9.2.3 Project Team Meetings

Scheduled meetings will be held and will include the protocol investigators and research staff involved with the conduct of the protocol.

During these meetings the investigators will discuss:

- Safety of protocol participants (adverse events and reporting)
- Validity and integrity of the data (data completeness on case report forms and complete source documentation)
- Enrollment rate relative to expectation of target accrual, (eligible and ineligible participants).
- Retention of participants, adherence to the protocol and protocol violations
- Protocol amendments

9.2.4 Audit Plan

The Yale Center for Clinical Investigation (YCCI) Office of Quality Assurance and Training will audit the trial at least annually or as determined by the YCC DSMC. The overall principal investigator, study coordinator and/or data manager may request access to all source documents and other study documentation for on-site or remote monitoring, audit or inspection.

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the Principal Investigator or Yale. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, and any applicable regulatory requirements.

9.3 Data Management

The investigators are required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. OnCore will be the designated electronic data capture tool. All data should be entered onto OnCore within 2 weeks of each study visit. AEs need to be entered within 72 hours and SAEs need to the entered within 24 hours of the site becoming aware of the event.

10.0 APPENDICES

10.1 ECOG Performance Status

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

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

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

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

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

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

* As published in the European Journal of Cancer:

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

In addition, volumetric analysis will be explored by central review for response assessment.

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