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TITLE: Moving PD-1 Blockade with Pembrolizumab into Concurrent Chemoradiation for Locally Advanced Non-Small Cell Lung Cancer

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1.0 TRIAL SUMMARY

Abbreviated Title	A Phase I Study of Pembrolizumab (MK-3475) and Concurrent Chemoradiation for Non-Small Cell Lung Cancer
Trial Phase	I
Clinical Indication	Inoperable Non-Small Cell Lung Cancer to be treated with Chemoradiation
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous
Trial Blinding	N/A
Treatment Groups	
Number of trial subjects	24-30
Estimated enrollment period	October 2015- March 2017
Estimated duration of trial	The trial will require approximately 18 months from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial from the time the Informed Consent Form (ICF) is signed through the final contact. Each eligible patient will receive treatment as per the trial design. After the end of treatment, each subject will followed every 8 weeks for adverse event monitoring or before the initiation of new anti-cancer therapy whichever comes first. Serious events and events of clinical interest will be collected for 90 days after the end of treatment. Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status every 12 weeks (±14 days) in the first year and every 16 weeks (±14 days) after year 1 until disease progression is confirmed by the investigator, a non-study treatment is initiated, consent is withdrawn, until death, or becoming lost to follow-up. All subjects will be followed by telephone for overall survival every 12 weeks (± 7 days) until death, withdrawal of consent, or the end of the trial.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a non- randomized, multi-site, open-label, Phase I trial of pembrolizumab (MK-3475) in subjects with locally advanced or inoperable non-small cell lung cancer, who have not received prior systemic chemotherapy or prior thoracic radiotherapy.

The main goal of this trial to assess safety and tolerability of the combination of pembrolizumab with curative intent chemoradiation therapy for non-operable non-small cell lung cancer.

Approximately 30 patients may be enrolled and will provide newly obtained formalin fixed paraffin embedded (FFPE) tumor biopsies for PD-L1 determination by immunohistochemistry (IHC). PD-L1 positive/negative population is defined as subjects with PDL-L1 assay result higher/lower than the PD-L1 cut point.

All subjects must have measurable disease based on RECIST 1.1. All patients will receive pembrolizumab regardless of PD-L1 status. Subjects will be administered pembrolizumab as per the study schema, starting at a dose of 100 mg and moving up to 200 mg every three weeks (Q3W), beginning after completion of chemoradiation and then incorporating pembrolizumab with chemoradiation as per the Phase I trial design.

Subjects will be monitored for toxicity through visits occurring weekly during radiation therapy and every week when receiving pembrolizumab alone.

Subjects will be evaluated at 9 weeks (± 7 days) after the first dose of pembrolizumab and every 9 weeks thereafter with radiographic imaging to assess response to treatment. Subjects will remain on treatment up to 18 doses of pembrolizumab. For follow-up after pembrolizumab, subjects will have imaging performed every 12 weeks thereafter. Images will be reviewed by the study investigators using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and the Immune Related Response Criteria (irRC) for determination of local response or metastatic progression. The investigator may choose to treat beyond RECIST 1.1 defined progression in subjects considered to be deriving clinical benefit and who are clinically stable.

Adverse events will be monitored through the trial and graded in severity according to the guidelines outlines in the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAEv4.0). Treatment with pembrolizumab will continue until documented disease progression by the investigator, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with the trial treatment of procedure requirements, completion of 18 doses of treatment with pembrolizumab or administrative reasons.

Subjects, who attain an investigator-determined confirmed complete response (CR), should continue for 18 doses of treatment. Subjects who discontinue for reasons other than disease progression or intolerability, or who discontinue after attaining a CR may be eligible for one year of retreatment after they have experienced radiographic disease progression. The decision to retreat will be at the discretion of the investigator only if no cancer treatment was administered since the last dose of pembrolizumab, the subject still meets the safety parameters listed in the Inclusion/Exclusion criteria and the trial remains open.

After the end of treatment, each subject will be followed for toxicities every 8 weeks (± 7 days) (for adverse event monitoring or before the initiation of new anti-cancer therapy whichever comes first. Serious events and events of clinical interest will be collect[redacted]

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Approval Date:
Expiration Date:

the end of treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status every 12 weeks (±14 days) in the first year and every 16 weeks (±14 days) after year 1 until disease progression is confirmed by the investigator, a non-study treatment is initiated, consent is withdrawn, until death, or becoming lost to follow-up. All subjects will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the trial.

The primary objective of this study is to evaluate the safety and toxicity of pembrolizumab in combination with definitive chemoradiation therapy for inoperable or locally advanced non-small cell lung cancer.

2.2 Trial Diagram

The trial design is shown in Figure 1

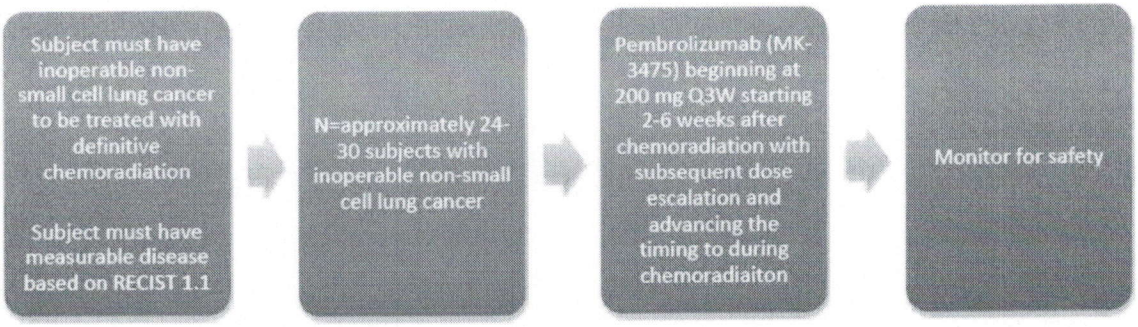

Figure 1 Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) Objective: To assess safety and toxicity of PD-1 inhibition with pembrolizumab with concurrent chemoradiation therapy for non-operable, locally advanced non-small cell lung cancer

Hypothesis: Intravenous administration of pembrolizumab will be safe and tolerable when incorporated into concurrent chemoradiation therapy

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: To evaluate local and distant metastasis-free survival, progression-free and overall survival with the addition of pembrolizumab to chemoradiotherapy

Hypothesis: The addition of pembrolizumab to chemoradiation therapy will result in improved progression-free survival, overall survival, and local and metastasis free survival rates over historical controls

(2) **Objective:** To evaluate the rates of pneumonitis that may result from combination pembrolizumab and chemoradiotherapy

3.3 Exploratory Objective

(1) **Objective:** To assess whether PD-L1 status on immunohistochemistry is predictive of response to pembrolizumab when combined with chemoradiation therapy

Hypothesis: Due to the potentiating effects of radiation therapy on the immune system, we hypothesize the improved response rates compared with chemoradiation alone will not rely on PD-L1 positivity alone. We expect PD-L1 patients to respond better than PD-L1 negative patients compared to chemoradiation alone.

(2) **Objective:** To assess T cell (CD8+T cells and CD4+FoxP3+ regulatory cells) responses at weeks 1, 3, 6 during chemoradiation therapy and before each administration of pembrolizumab for cycles 1, 2, 3

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

In 2014, an estimated 224,210 individuals will have been diagnosed with lung cancer, and this diagnosis will result in approximately 159,260 deaths(1). The elevated mortality of this disease suggests both a poor biology and inadequacy of available therapies. At presentation, most non-small cell lung cancer (NSCLC) cases are medically inoperable or have unresectable disease. Locally advanced disease and metastatic disease each account for about 30% of all new diagnoses, implying that resectable disease is a minority of NSCLC (<20%)(2). Management of medically inoperable and locally advanced NSCLC relies on radiation therapy as the primary modality of therapy and is usually combined with concurrent chemotherapy, which has shown the greatest promise with regard to overall survival in numerous randomized trials (3, 4).

Despite the known efficacy of radiation therapy in the setting of locally advanced or medically inoperable NSCLC and the improvements in the technical aspects of radiation therapy delivery (5), the treatment outcomes leave significant room for improvement. Median survival rates according to randomized trials are in the range of 20-28 months. Historically, 5-year survival rates are 10-15%. Local recurrence rates occur in 50-70% of cases (6, 7), and local failures correlate with diminished survival (8).

The current standard of care for locally advanced medically inoperable NSCLC is combined modality radiation therapy with concurrent platinum based doublet chemotherapy. The standard RTOG regimen for chemoradiotherapy consists of carboplatin (AUC=2) and paclitaxel (50 mg/m^2) both delivered weekly with 60 Gy of radiation therapy delivered in 2 Gy daily fractions. These treatments are well tolerated with expected toxicity rates of neutropenia, dermatitis, esophagitis, pneumonitis (about 20%-30%).

4.2.1.1 Rationale for PD-1 Blockade with Radiation Therapy

The combination of radiation therapy and immunotherapy is a promising new treatment strategy in solid tumors. Radiation therapy generates an immune response with the increased presentation of antigens via MHC Class I and subsequent T cell recognition of irradiated cells (9). Despite radiation therapy stimulation of the immune system, an immunologic equilibrium results whereby tumor attack after radiation therapy diminishes. PD-1 blockade enhances further tumor destruction by limiting the state of anergy and provides a potential springboard for achieving an improvement in the cure for these patients.

Inhibition of PD-1 may permit improved tumor rejection. For example, using PD-1 deficient TCR Tg T cells, the absence of PD-1 was associated with marked improved tumor rejection in vivo, even with CTLA-4 deficient T cells did not reject (10). Likewise, polyclonal antibody against PD-L1 can promote tumor rejection in models (11). PD-1 is expressed directly on tumor cells and therefore makes it an attractive target for immune-mediated responses. It

therefore follows, that PD-1 blockade will promote tumor rejection by limiting immune anergy and will permit immune-mediated interpretation of a neoplasm as foreign signal warranting attack.

Liang et al demonstrated that the differential response of tumor to RT in individual mice is correlated with the magnitude of the T cell response to tumor antigens. Ag-specific T cell responses were significantly increased in the radiation group compared with the unirradiated group. T cell responses were lower in animals with stable disease. It was found that ablative radiation therapy increases the frequency of Ag-specific CD8+ T cells that infiltrate the tumor, but both overall T cell infiltration and cytokine production decrease over time in the tumor microenvironment, producing radiation-induced tumor equilibrium. This equilibrium can be combatted by blocking PD-1 using a neutralizing antibody to release suppression of PD-1+T cells within the tumor microenvironment to result in tumor rejection in the setting of irradiated tumors (12). Verbrugge et al have corroborated similar findings (13). Therefore radiation induced tumor equilibrium can be disrupted to yield complete regression of tumors using PD-1 blockade.

4.2.1.2 Data Supporting Concurrent Immunotherapy and PD-1 Blockade with Concurrent Chemoradiation

Available preclinical data about immunotherapy concurrent with radiation suggest a benefit to combining immunotherapy during radiation therapy. For example, Dewan and colleagues demonstrated that fractionated radiotherapy was able to cause shrinkage of tumors outside of the radiation field when combined during CTLA blockade. When CTLA blockade or radiation therapy was used alone, then the effects on the primary and distinct secondary disease demonstrated less response than concurrent therapy (14).

Similarly, anti-PD-1 blockade with stereotactic radiation is able to produce long-term survival in murine glioma models. When concurrent therapy was used, the brains of mice harbored significantly increased CD8 effector T cells compared to mice that did not receive radiation. Therefore, the blockade of PD-1 allowed for synergism with radiotherapy. Also of interest, is the apparent "cure" with PD-1 in the experimental portion of the study; mice that survived more than 90 days after cranial RT, and then when re-challenged with malignant cells did not develop recurrence, suggesting systemic immunity. In contrast, mice without prior exposure to PD-1 developed tumor growth after re-challenge (15).

PD-L1 expression in the tumor microenvironment has been associated with poor outcomes after chemoRT (16). Deng et al described that local upregulation of the PD-L1/PD-1 axis after RT suppresses immune responses, which then limits the full expression of antitumor immunity and can lead to relapse. By combining RT and PD-L1 blockade, antitumor immunity is optimized and leads to the elimination of myeloid-derived suppressor cells via T-cell-derived TNF. PD-L1 blockade enhances RT by alleviating the inhibitory action of PD-L1 on t cells and treats the primary tumor as well as metastatic (both gross and occult) disease in distant

sites (17). Likewise, in a breast cancer model, Treg cell ablation with PD-1 blockade with tumor irradiation significantly reduced tumor burden and improved overall survival compared to Treg inhibition alone (18).

In breast cancer and melanoma models studied by Sharabi et al (19), it was found that radiation therapy induced endogenous antigen-specific immune responses with combined with anti-PD-1 checkpoint blockade immunotherapy. Immune-stimulating effects of radiation therapy were increased when radiation therapy was combined with anti-PD-1 therapy, resulting in the development of antigen-specific T cell and B cell-mediated immune responses. RT increased the percentage of antigen-experienced T cells and effector memory T cells. RT also upregulated tumor-associated antigen-MHC complexes, enhanced antigen cross-presentation in the draining lymph node and increased T-cell infiltration into tumors.

Therefore, the available preclinical data supports the use of concurrent PD-1 blockade with concurrent RT, as PD-1 inhibition changes the tumor microenvironment to reduce Treg cell function and improve the efficacy of RT. This combination of PD-1 inhibition and radiation therapy can prime endogenous antigen-specific immune response and provide an additional mechanistic rationale for combining radiation with PD-1 blockade.

4.2.1.3 **Clinical Data in Support of Combined PD-1 Inhibition, Chemotherapy, and Radiation Therapy for Non-Small Cell Lung Cancer**

It is apparent that the role of the immune system response is paramount in the overall outcome for the patient. In a set of non-small cell lung cancers (NSCLC), CD3 or CD8+ Tumor-infiltrating lymphocytes (TILs) were associated with better outcome in NSCLC (20). Recent studies incorporating immunotherapy with lung cancer have demonstrated great promise. A study of MK-3475 monotherapy for previously treated non-small cell lung cancer demonstrated objective response rates of 24% by immune-related response criteria (irRC) and 21% by RECIST1.1. Median duration of response by irRC was not reached at a median duration of follow-up of 62 weeks (21). Also, nivolumab has recently been shown to have single agent activity in squamous cell carcinoma of the lung after demonstrating a 14.5 % objective response rate and median time to response of 3.3 months with a median duration of response that has not yet been reached (22).

The START trial specifically addressed the question of immunotherapy after chemoradiotherapy using a MUC1 antigen-specific immunotherapy (tecemotide). Also median overall survival rates were not significantly different with tecemotide versus placebo, but for those who received prior concurrent chemoradiotherapy, the median overall survival was 30.8 months with adjuvant tecemotide versus 20.6 months for those who received adjuvant placebo (23) and suggests a synergy between chemoradiotherapy and immune modulation. A 3% rate of pneumonia was seen.

Evaluating the possible combination of chemoradiation and PD-1 blockade in locally advanced NSCLC is of great importance given the relatively poor survival out[redacted]

metastatic disease, and suggestion that radiotherapy with PD-1 inhibition has potential for synergism. Herein, we propose a trial moving PD-1 blockade into chemoradiation in a phase I study, given the possible risk of pneumonitis with both therapies.

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

The primary objective of this trial is to characterize the safety and tolerability of pembrolizumab in subjects with inoperable/locally advanced NSCLC treated with chemoradiation therapy. The primary safety analysis will be based on subjects who experience toxicities based on CTCAEv4.0 criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab including serious adverse events (SAEs) and events of clinical interest (ECIs).

Safety will be assessed by reported adverse experiences using CTCAEv4.0. The attribution to drug, time-of-onset, duration of the event, its resolution and any concomitant medications administered will be recorded. ACs will be analyzed including but not limited to all AEs, SAEs, fatal AEs and laboratory changes. Furthermore, specific immune-related adverse events (irAEs) will be collected and designated as immune-related event of clinic interest (ECIs).

4.2.3.1 Efficacy Endpoints

The primary goal of this trial is to evaluate the safety and tolerability of pembrolizumab in combination with chemoradiation therapy for inoperable/locally advanced NSCLC.

A secondary objective is to evaluate local and metastasis-free survival, progression-free and overall survival. Overall response rate based on RECIST1.1will be assessed by the investigators. Subjects must have measurable disease. Response rates will be compared to historical results.

4.2.3.2 Biomarker Research

Subjects will be required to have newly obtained core or excisional tumor biopsies to support the ability to investigate the correlation between PD-L1 protein expression by immunohistochemistry and the anti-tumor activity of pembrolizumab in locally advanced NSCLC. If a relationship can be ascertained, then a threshold for optimal prediction of response can be determined.

Subjects will be enrolled on this trial regardless of PD-L1 expression. Thus tissue availability but not high biomarker expression is required for trial entry. This data will be of importance given the novelty of the combination of pembrolizumab concurrent with chemoradiation.

Subjects will also undergo evaluation of T cell responses at weeks 1, 3, 6 during chemoradiation therapy and before each administration of pembrolizumab for cycles 1, 2, 3. Due to the expected immune stimulation from combination chemoradiation therapy and pembrolizumab, it is likely that this combination will result in increased effector CD8+ Tcells and decrease in CD4+FoxP3+ regulatory cells. These levels will be measured via flow cytometry.

4.3 Exploratory Objective

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects at least 18 years of age with inoperable non-small cell lung cancer who are eligible for chemoradiation therapy will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

1. Written informed consent and HIPAA authorization for release of personal health information

2. Age $\geq$ 18 years at the time of consent

3. Subjects with any kind of NSCLC histology documented by histology or cytology from bronchial brushing or washing, or needle aspiration of a defined lesion but not from sputum cytology alone.

4. Must have AJCC 7th ed. inoperable Stage II disease requiring chemoradiation therapy or stage IIIA or IIIB NSCLC based on appropriate staging studies including brain MRI or head CT, CT Chest, and FDG-PET/CT scan..

5. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. Newly-obtained is defined as a specimen obtained up to 35 weeks (250 days) before initiation of treatment on Day 1. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the Sponsor or may undergo Fine needle aspiration.

6. ECOG performance status of 0 or 1 within 14 days before registration for protocol therapy.

7. Adequate laboratory values obtained within 14 days before registration for protocol therapy.

Table 1 Adequate Organ Function Laboratory Values

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

8. Forced expiratory volume ≥ 1.0 L or ≥ 40% of predicted with or without bronchodilators by pulmonary function testing.

9. Women 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.

10. Women 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.

11. 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.

12. Have measurable disease based on RECIST1.1

5.1.3 Subject Exclusion Criteria

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 systemic steroid therapy or any other form of immunosuppressive therapy within 7 days before the first dose of trial treatment.

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 adverse events due to agents administered more than 4 weeks earlier.

6. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

   - Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

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

7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or 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 not participate.

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

11. Evidence of interstitial lung disease.

12. Has an active infection requiring systemic therapy.

13. 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.

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

15. 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.

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

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

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

19. Has received a live vaccine within 30 days of planned start of study therapy.

20. Pleural effusion that cannot be controlled despite appropriate interventions.

21. History of allergy or hypersensitivity to any component of the treatment.

22. No active second cancers.

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 or 100 mg depending on trial schema in Section 5.3	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental

Treatment will continue for up to 12 months, in the absence of prohibitive toxicities or disease progression.

Trial treatment should begin on the day of enrollment or as close as possible to the date on which treatment is allocated/assigned.

5.2.1 Dose Selection/Modification

The dose amount required to prepare the Pembrolizumab infusion solution is a fixed dose as per Table 2 of either 100 mg every 3 weeks or 200 mg every 3 weeks.

5.2.1.1 Dose Selection

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

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

5.2.1.2 Dose Modification

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose

or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.6.1 and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids.

Table 3. Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

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

Immune-related AEs	Toxicity grade or conditions (CTCAEv 4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Grade 4	Permanently discontinue		

[redacted] IRB
IRB ID:
Approval Date:
Expiration Date:

AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg. levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

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

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

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

5.2.2 Timing of Dose Administration

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 100 mg or 200 mg will be administered as a 30 minute IV infusion every 3 weeks as per trial design. 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

A schema to evaluate the safety of administering pembrolizumab with chemoradiation (CRT) is provided below. Successive regimens have progressively longer concurrent treatment times going from post radiation, to 2 weeks overlap, to 6 week overlap if tolerated or increase MK-3475 from 100 mg Q 3 WEEKS to 200 mg Q 3 WEEKS. The safety is evaluated through dose limiting toxicity (DLT) consisting of grade 4 pneumonitis. The 3+3 design with dose de-escalation and starting at Regimen 1 will be used to find the maximum tolerated dose (MTD) regimen. After MTD is found, six more patients will be treated at MTD dose regimen for a better evaluation of the safety of the dosing schedule for further study. The details of the 3+3 design with dose de-escalation are shown below.

Day 0 is the start day for chemoradiation (CRT)

Day 42 is the presumed last day of chemoradiation

Table 4: Trial Design

START of PEMBROLIZUMAB	Day of starting pembrolizumab	Pembrolizumab Dose	Regimen
2-6 WEEKS AFTER CRT	Day 56-84	100 mg Q3 WEEKS	-1
2-6 WEEKS AFTER CRT	Day 56-84	200 mg Q3WEEKS	1

2 WEEKS BEFORE END OF CRT	Day 28	100 mg Q3WEEKS	2
2 WEEKS BEFORE END OF CRT	Day 28	200 mg Q3WEEKS	3
AT START OF CRT	Day 0	100 mg Q3WEEKS	4
At start of CRT	Day 0	200 mg Q3WEEKS	5

A 3-week Dose Limiting Toxicity period will be observed after each dose level is completed, and before subjects are enrolled to the next dose level.

With starting dose regimen 1, groups of 3 patients will be entered at a dose level:

- If all 3 patients treated at the dose regimen do not have a dose limiting toxicity (DLT), then the dose will be escalated to the next dose regimen.
- If 1/3 patients have DLT, then 3 more patients will be treated at this dose level. If none of these additional patients has DLT, then the dose will be escalated, otherwise three more patients are treated at the prior dose regimen (if at most 3 patients were previously treated at that prior dose regimen).
- If at least 2/3 patients have DLT, then three more patients are treated at the prior dose regimen (if at most 3 patients were previously treated at that prior dose regimen).

The MTD is the dose regimen that 0/6 (or 0/3 if at dose level –1) or 1/6 patient experience DLT; and at least 2/3 or 2/6 patients treated with the next higher dose regiment will have had DLT.

Note: If the escalation occurs at the last dose regimen (Regimen 5), then the MTD is at or above the last dose regimen. If the de-escalation occurs at dose regimen -1 (at least 2 out of 3 patients or at least 2 out of 6 patients have DLT at dose regimen -1), then the MTD is below the dose regimen -1. In either case, the MTD is not determined from the trial. But for the former, the last regimen (Regimen 5) is safe and still can be used safely for further studies.

5.4 Stratification

No stratification will occur in this trial.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

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

5.5.1 Acceptable Concomitant Medications

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

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

5.5.1.1 Radiation Therapy Administration

The use of image guided radiation therapy is highly encouraged but not required.

Radiation and Chemotherapy must both begin on day 1.

5.5.1.2 Radiation Dose Specifications

The total dose will be 60 Gy in 30 fractions of 2 Gy. Radiation treatment will be administered 5 days per week, 1 fraction per day. It is recommended that radiation treatment begin on a Monday or Tuesday. There are no field reductions. All fields must be treated daily and the entire PTV must be treated daily. Radiation therapy (RT) commences on day 1 of chemotherapy.

The treatment plan will be normalized such that 95% of the PTV is covered by the prescription dose. No more than 0.03 cc of the PTV may receive > 120% of the prescription dose (maximum dose constraint).

5.5.1.3 Technical Factors/Treatment Planning

Beam Energy: 6 - 15 MV will be used. Multi-leaf collimation (MLC) or individually-shaped divergent custom blocks will be used to spare normal tissues outside of the target volume. 3D Conformal Radiation Therapy (3D-CRT) or Intensity-Modulated Radiation Therapy (IMRT): The PTV is to be treated with any combination of coplanar or noncoplanar fields optimized to deliver the specified dose while restricting the dose to the normal tissues. Each field is to be treated daily throughout the course of treatment. All radiation doses will be calculated with heterogeneity corrections that take into account the density differences within the irradiated volume.

5.5.1.4 Localization, Simulation, and Immobilization

Immobilization to assure reproducibility of the setup is necessary. Each patient will be positioned in an immobilization device in the treatment position on a flat table. A volumetric treatment planning CT study will be required to define gross tumor volume (GTV), internal target volume (ITV), clinical target volume (CTV), and planning target volume (PTV)(see definitions below). Contiguous CT slices, having no more than 3 mm thickness through the regions harboring gross tumor and grossly enlarged lymph nodes and no more than 10 mm thickness of the remaining regions are to be obtained starting from the level of the cricoid cartilage and extending inferiorly through the entire liver volume. The GTV, CTV/ITV, and PTV and normal organs will be outlined on all appropriate CT slices. Intravenous (i.v.) contrast during the planning CT is optional provided a diagnostic chest CT was done with contrast to delineate the major blood vessels. If not, IV contrast should be given during the planning CT.

5.5.1.5 4-D CT planning

The use of four-dimensional radiation treatment planning is highly encouraged. Acceptable methods of accounting for tumor motion include: design of the PTV to cover the excursion of the primary and involved nodal CTV during free breathing (motion inclusive), or the more limited excursion during a voluntary or automatic breath-hold (e.g., Elekta ABC device) or a gating approach (e.g., Varian RPM system).

5.5.1.6 Target Volumes/Motion Management Target Volumes

□ Definition of the GTV: The primary tumor and clinically positive lymph nodes seen either on the pretreatment or the planning CT (> 1 cm short axis diameter) or pretreatment PET scan (maximum SUV > 3) will constitute the GTV. Pathologically involved nodes not meeting radiographic criteria also should be included in the GTV. The volume(s) may be disjointed. In the event of a collapsed lobe or lung segment, the use of PET to distinguish tumor from fluid/atelectasis is encouraged.

□ Definition of the CTV: The CTV is defined to be the GTV plus a 0.5 cm to 1 cm margin as appropriate to account for microscopic tumor extension. However, the CTV should not cross natural anatomic barriers to tumor extension such as fissures or fascial planes unless these structures are directly abutted or invaded by the GTV. Elective treatment of the mediastinum and supraclavicular fossae will not be done.

□ Definition of the PTV: The internal target volume (ITV) is defined to be the CTV plus an internal margin (IM) to account for target/organ motion. The final PTV is defined to be the ITV plus a setup margin (SM) to account for patient positioning uncertainty and machine tolerance. These margins are determined as described below.

5.5.1.7 Critical Structures

Normal tissue constraints shall be prioritized in the following order for treatment planning: 1=spinal cord, 2=lungs, 3=esophagus, 4=brachial plexus, and 5=heart.

Spinal Cord: The spinal cord should be contoured based on the bony limits of the spinal canal from the top of C1 to the bottom of L2. The spinal cord dose limit is the highest priority dose constraint and thus must be met irrespective of other constraints. No more than 0.03 cc of the spinal cord may receive greater than 50.5 Gy total dose.
Lungs: The total lung volume is defined as the sum of the volume of both lungs minus the GTV. The dose-volume constraint to the lungs is the second highest priority and must be met, except if it conflicts with the cord dose constraints. The proportion of total lung volume that receives more than 20 Gy (V20) should not exceed 31%. Additionally, the mean lung dose should not exceed 20 Gy.
If either of these constraints is exceeded, for the 3D-CRT cases, one might increase the weighting of any AP/PA fields and reduce any oblique fields. This can be done as long as the cord dose (above), which takes precedence, is not exceeded. For 3D-CRT or IMRT cases, one can reduce the CTV to the minimum range suggested above especially near the spinal cord.
Esophagus: The esophagus contour should include the mucosal, submucosa, and all muscular layers out to the fatty adventitia, from the bottom of the cricoid cartilage to the gastroesophageal junction. No more than 0.03 cc of the esophagus may receive > 63 Gy. The mean dose to the esophagus should be ≤ 34 Gy. The esophagus should not be circumferentially irradiated with > 60 Gy (i.e., the 60 Gy isodose line should not encompass the entire axial cross-section of the esophagus at any level)
Brachial Plexus: The ipsilateral brachial plexus should be contoured for upper lobe tumors. No more than 0.03 cc of the brachial plexus may receive > 63 Gy.
Heart: The heart and pericardium should be contoured together from the base to the apex of the heart. The following limits are recommended: V60 to <1/3, V45 to <2/3, and V40 to <100% of the heart.

5.5.1.8 Proton Beam Therapy

Use of Proton Beam or Photon Therapy will be permitted as per investigator decision.

Proton dose will be reported in Gy (relative biological effectiveness, RBE), where 1 Gy (RBE) = proton dose Gy x RBE , RBE = 1.1.

5.5.1.9 Dose Specifications

Dose Prescription
□ Patients in both proton and photon arms will receive treatments 5 days per week using 2 Gy (RBE) per fraction. RBE used will be 1.1 for protons and 1 for photons. The total prescribed dose will be 60 Gy (RBE) **without exceeding tolerance dose-volume limits of all critical normal structures. If difficulty achieving dose tolerances priority should be set to achieve tolerances to normal organs and compromises can be made for margins (CTV, ITVs, PTVs) as deemed appropriate by the treating radiation oncologist. Lung doses should take priority in being kept to a minimum.**
□ Dose distribution will be normalized to cover 95% of the PTV with the prescription dose.
□ A volume of no more than 0.03 cc inside PTV should exceed 120% of the prescribed dose.
□ 100% of the ITV (motion-incorporated CTV) must be covered by the prescription dose.
the prescription dose

5.5.1.10 Technical Factors

□ Proton therapy may be delivered using passively scattered protons or using scanning beam.
o Selected proton energies should be high enough to adequately provide target coverage. Range shifters may be used to make fine adjustment to the maximum proton range.
o Both passive scattering and scanning beams may employ apertures and/or compensators, as appropriate, to shape the fields laterally and distally.

5.5.1.11 Simulation, Immobilization

Simulation
Motion assessment must be performed on all patients to determine the motion management technique and the appropriate type of treatment planning CT required.

A motion management technique-specific treatment planning CT (e.g., 4D, breath-hold, with ABC device, etc.) will be required during simulation to define gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV). Contiguous CT slices, having no more than 3 mm thickness are to be obtained starting from the level of the

cricoid cartilage and extending inferiorly through the entire liver volume. The field of view must be large enough so that none of the patient's anatomy along the path of the treatment beams is cut off.

A CT scanner unit calibrated for proton treatments with the appropriate proton relative linear stopping power (RLSP) vs. HU conversion function shall be used for simulation.

Intravenous contrast during the planning CT is optional provided a diagnostic chest CT was done with contrast to delineate the major blood vessels. If not, intravenous contrast should be given during the planning CT. If contrast is used, the densities should be over-ridden or the contrast scan must be registered to a non-contrast scan for planning purposes.

Immobilization
Patients will be positioned in a stable position capable of allowing accurate reproducibility of the target position. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments.

A variety of immobilization systems customized to the participating institutions standard of practice may be used, including using an alpha-cradle or vac-bag. Stereotactic frames that surround the patient on 3 sides and large rigid pillows (conforming to patients' external contours) may be used as indicated.

Techniques for motion management will be employed as per the institutional standard for proton beam therapy. See Section 5.5.1.5 for 4D-CT.

5.5.1.12 Target Definitions, Target Delineation, and Normal Anatomy Delineation

Target Definition
□ GTV: Gross tumor volume is all known gross disease as demonstrated on the single phase planning CT, and modified as deemed necessary based on PET and other imaging studies.

□ iGTV: GTV plus margin for tumor motion, which isthe union of the GTVs on all respiratory correlated images, or the gross tumor volume contoured directly on maximum intensity projection (MIP) images. The delineated iGTV will be compared with the actual position of the GTV on each of the respiratory correlated CTs and modified, if necessary, to encompass the extent of motion of the GTV (hence iGTV). The iGTV may also be modified as deemed necessary based on PET and other clinical studies that may better distinguish the true GTV from other near unit density tissues. (If a breath-hold technique is used, iGTV is the union of the GTVs on 3 breath hold scans-see below)

□ CTV: Clinical target volume is the subclinical involvement around the GTV. The CTV is the GTV plus an 8-mm margin for micro extensions of the tumor (CTV=GTV+8 mm) without extending into uninvolved organs, such as the esophagus, heart, or bone.

□ ITV: ITV=iGTV+8mm Internal target volume is the union of the CTV plus motion or iGTV plus 8 mm CTV. The ITV may equivalently be created in one of two ways: (1) by expanding the iGTV by 8 mm to include subclinical microscopic disease without extending into uninvolved organs, such as the esophagus, heart, or bone; or (2) by combining all CTVs in all respiratory phases. This volume will be reviewed and edited according to patient's anatomy by the treating radiation oncologist, according to the prevailing current clinical practice standard.

□ PTV: Planning target volume is ITV plus a margin to ensure that the prescribed dose is actually delivered to the ITV. This margin accounts for variations in treatment delivery, including variations in setup between treatments. The ITV is expanded isotropically by 35 mmto generate the PTV. The PTV, defined in this manner, is relevant to photon planning and for
plan evaluation for both protons and photons.

5.5.1.13 Target Delineation
□ The simulation CT scan images will be used for target delineation and treatment planning. The proper lung window should be used for target delineation in the lung parenchyma, and proper soft tissue window should be used to delineate the nodal disease.

□ iGTV should be contoured on the maximum intensity projection (MIP) images when 4D CT simulation is done. Or, the iGTV should be created by combining the GTV contours delineated in inhale and exhale scans.

Motion management scenarios as specified in the table below:

Motion Management	**Scans**	**Scan to be used for dose calculation**	**Images from which the target volume contours are to be generated**
4-D CT simulation with free breathing	1 free breathing scan, 1 4D scan (10 imaging data sets)	AVG of all phases	MIP or union of the GTVs of all phases used to generate gross tumor plus tumor motion=iGTV, iGTV+CTV (5-8mm)=ITV ITV+5mm=PTV
4-D CT simulation with free breathing gating	1 free breathing scan, 1 4D scan (10 imaging data sets	AVG of the beam-on phases (e.g. 40-60%)	Union GTVs contoured at each breathing phase wile

			the beam will be on (e.g. 40-60%) =iGTV iGTV+CTV (5-8mm)=ITV ITV+5mm=PTV
4-D CT simulation with breath hold (with or without ABC)	Repeat breath hold scan 3 times to assess reproducibility of the breath hold.	Select one scan for dose calculation	Union of GTVs contoured at each breath hold scan =iGTV iGTV+CTV (5-8mm)=ITV ITV+3-5mm=PTV

5.5.1.14 Treatment Planning and Quality Assurance
For protons, average of all scans used will be employed for dose calculations, compensator and aperture design and plan evaluation. However, individual phases may also be used for evaluating dose distributions.

5.5.1.15 Planning Procedures – Protons
□ Passively scattered proton therapy (PSPT) or scanned proton beams will be used for patients enrolled in the proton arm.
□ For proton planning, each beam has an individual and unique PTV expansion from the ITV. In the plane perpendicular to the proton beam axis, the PTV expansion from the ITV is according to the method used for photons. However, along the direction parallel to the proton beam axis, the distal and proximal margins to expand the ITV will be computed using established algorithms based on range uncertainty of the beam. For multiple ITVs, the most distal edge of the collection of ITVs is assigned range uncertainty margin.
□ To compensate for the perturbation of the proton dose distribution due to misalignment of the compensator and the anatomy, the compensator is smeared. The smearing radius will be calculated using the algorithms established at each participating institution (Moyers 2001). The compensator may be smoothed to reduce hot spots.
□ A block margin must be assigned depending on the penumbra specific to the proton beam being used. Note that proton beam penumbra is a function of proton energy and the distance between aperture + compensator and patient's anatomy. It may vary significantly from one clinical situation to another.
□ **Note:** While the treatment planning parameters, including distal and proximal margins, block margin and the smearing radius may be calculated based on published formulae, (Moyers 2001) they may be modified for the local machine characteristics and practice. Variation of magnitudes in these parameters from one institution to another is acceptable; however, the parameters selected must ensure specified target coverage and normal tissue sparing in the face of range and set up uncertainties.

5.5.1.16 Critical Structures Constraints

□ Dose volume constraints for normal critical structures are given in the Table below. These dose values can be used as guidelines for constraining the optimization process during treatment planning, and they are also used for scoring each case for protocol compliance

□ For superior sulcus tumor or upper lobe tumors where the brachial plexus is part of the target volume, the volume receiving 70 Gy (V70) can be as large as 10 cc with significant areas within receiving doses as high as 74 Gy.

□ If any portion of cardiac structure is part of the planning target volume (PTV), respiratory gating or another technique to separate cardiac structures from the PTV and allowing the full prescription dose to be delivered should be the first stepDoses exceeding the limits of variation acceptable listed in the Table below will be considered a deviation unacceptable.

Critical Structure Dose Constraints and Compliance Criteria

	Per Protocol	Variation Acceptanle*
Normal lung (right ling + left lung minus GTV)	V20 ≤ 31%; MLD ≤ 20 Gy (RBE); lung V5 ≤ 60%	V20 ≤ 35% or MLD ≤ 22 Gy (RBE); lung V5 ≤ 65%
Esophagus	Max dose: 74 Gy (RBE) ≤ 1cc of partial circumference	Max dose: 74 Gy (RBE) ≤ 1.5 cc of partial circumference
Brachial Plexus**	V70 ≤ 3.0 cc V74 ≤ 1.0 cc V75 ≤ 0.5 cc	V75 ≥ 0.5 cc
Spinal Cord**	V50 < 0.03 cc	V52 < 0.03 cc
Heart	V30 ≤ 50% V45 ≤ 35%	V30 ≤ 55% V45 ≤ 40%

* Doses not meeting the Variation Acceptable limits will be classified as Deviation Unacceptable.

** See first bullet in the list just above the Table for exception to the values for this critical structure.

*** See the last bullet in the list just above the Table for exception to the values for this critical structure.

**** When this value cannot be achieved, treatment plans must be modified to move dose distribution hotspots away from the heart to avoid having the case scored as a Deviation Unacceptable.

5.5.1.17 Image Guided Treatment

□ Image-guided radiation therapy (IGRT), consisting of images and appropriate image alignment software tool, is required for both photon and proton treatments on this protocol. It is expected that investigators will be familiar with those concepts presented in the ASTRO

IGRT White paper (Jaffray in press).
□ Patients will be treated only on units with image guidance capabilities. Such units include ones with on-board imaging, CT-on-rails, or other dedicated imaging system for patient positioning. At a minimum, these units must include orthogonal x-ray imaging systems for patient positioning and employ software tools for image registration.
□ To achieve compliance with the PTV expansions stated in the protocol, daily imaging is required.

5.5.1.18 Mid-Course Repeat CT Scans to Adapt Radiotherapy to Anatomic Changes

Repeat CT acquisition

□ In addition to the CT datasets obtained for planning of treatments, repeat CT scans will be performed to assess whether a patient requires modifications to their treatment plan. The initial simulation planning scan should be scheduled to occur as close as possible to the starting date and no more than 21 days prior to the estimated treatment start date. If the starting date is 14 days or more from the simulation date, a pre-treatment verification CT scan is strongly recommended. Additional repeating studies must occur during the time the dose delivered is between 20-24 Gy and between 46-50Gy.

□ Repeat CTs will be of the same type (4D, breath-hold, etc.) as the initial planning CT depending upon the motion management strategy being used.

Determination of the need for replanning

□ The repeat CT scan will undergo a rigid fusion with planning-CT and the targets from the original simulation scan and OARs will be transferred to the repeat CT scan. The same fusion technique used for daily IGRT (bone matching, soft tissue matching, drag-and-drop) will be used for image registration of the repeat CT scans. Rotational changes to the fusion should only be done if the institution has the equipment needed to implement this type of adjustment as part of its daily IGRT system.
□ The GTV or iGTV, spinal cord, lungs and other OARs will be reviewed by a physician and will be modified as needed. Any modifications to an OAR must be denoted by the structure name followed by the sequence number of the scan (1 or 2,
depending on which of the three repeat scans is currently being evaluated). GTV or iGTV do not require modifications, unless they lie > 3mm outside the originally contoured GTV or iGTV. GTV or iGTV should be re-contoured if tumor regression develops within the previously contoured region, but the CTV (or ITV) and PTV should remain the same. Recontouring may also be necessary if the GTV shifts relative to other anatomy or deforms. In this case the CTV should be adjusted to the new iGTV/GTV + margin, and a new PTV should be created.
Important note: Even though the GTV may shrink substantially during the course of radiotherapy, the CTV is assumed to retain its volume. Therefore, the CTV (or ITV) should not be reduced even if the GTV or iGTV has regressed in the repeat CT scans. The assumption is that there is likely to be microscopic disease present where GTV or iGTV was. The CTV (or ITV) shape may change depending on changes in the surrounding anatomy.

□ The beam configuration (beam directions, energies, SOBPs, weights, compensators, apertures, etc.) from the previously approved treatment plan will be transferred to the repeat CT, the dose distribution will then be recalculated, and a new set of DVHs will be created for the OARs and target structures.

Verification plan and replanning (adaptive planning)
A verification plan is a plan with dose distribution computed using the new repeat image and the original (or the current beam) configuration to verify whether the dose distribution is still acceptable. An adaptive plan is a new plan designed to meet the specified criteria. It will very likely have a different beam configuration. The treating physician should evaluate the verification plan and decide on the need of replanning. When there is an unfavorable change in dose distribution to an OAR or target in the verification plan, every effort is made to restore the DVH for that structure to the previous/original plan's DVH. At times this is not achievable, but that is the goal of replanning.
□ The following steps should be taken to evaluate verification plans and create the adaptive plans:
o Use the original plan on the original scan to full prescription dose as reference
o Create the dose distribution from the original plan with the full prescription dose on the replanning scan. This is done to evaluate if there is any change in DVH on the replanning scan if the original plan is delivered in full.
o If replan is indicated, create an adaptive plan on the new scan with the remaining dose and this will be used to deliver the rest of the treatment or until another replan is indicated.
□ Target coverage: Replanning of a treatment plan based on under coverage of the target must be performed if the target coverage shows deviation unacceptable in verification plan.
□ OAR overdose: Replanning of a treatment plan based on higher doses to the OARs must be performed if the spinal cord Dmax(0.03cc)>52 Gy, lung V20>35%, or mean lung dose >20Gy.
□ Inferior dose distribution compared with the original plan: Replanning of a treatment plan should be done when the verification plan is inferior to the original plan. For example, MLD 17 Gy in the verification plan when MLD was 12 Gy in the original plan in the event that the tumor becomes cavitary or had significant reduction causing overshooting into the normal lung. Another example would be proton overshoot to heart due to tumor regression.
□ For other, less critical tissues, if the dose calculated with the original beam configuration to the new image indicates unacceptable deviation based on criteria specified in the Table in Section 6.5.4, replanning will be at the discretion of the treating physician.
□ Dose distributions displayed on each of the modified plans are used for evaluation and delivery of the remainder of the treatments. The dose delivered to date is not considered in the design and optimization of the new plan. The new plan, on its own, should meet the specified target coverage and normal tissue criteria.
□ For patients requiring adaptive plans, the following procedure is to be used to estimate the summed dose distributions. Beam configurations for the original and the adaptive replans used for treatments will be applied to the CT image of week 5, assumed to represent an

average anatomy over the course of radiotherapy. The dose distributions computed for each of the configurations will be summed weighted according to the number of fractions each distribution was used.

5.5.1.19 Radiation Therapy Adverse Events

Reversible or permanent alopecia, bone marrow toxicity, skin pigmentation, and esophagitis are expected side effects of radiation therapy. Radiation induced myocarditis or transverse myelitis rarely occur at doses lower than 50 Gy. Radiographic evidence of radiation change and subsequent fibrosis of the lung will occur within lung volume receiving $\geq$ 20 Gy, usually within the first 6 months and most often within the first 2-3 months after initiation of treatment. It is essential to spare as much normal lung as possible in order to avoid symptomatic lung injury.

5.5.1.20 Esophagitis

Esophageal complaints are common with combined modality therapy. Esophagitis does not constitute a reason to interrupt or delay radiotherapy or chemotherapy provided oral intake is sufficient to maintain hydration. Patients should be advised to avoid alcoholic, acidic, or spicy foods or beverages. Viscous Xylocaine, Carafate or other medications should be used for symptomatic relief. Occassionally, narcotics may be required.

Acute esophagitis may persist for 4-6 weeks. If Grade 4 (CTCAE, v. 4) esophagitis occurs, and a treatment interruption is being considered, every effort should be made to limit it to 3 treatment days or less. Patients requiring hospitalization because of esophagitis may have their treatment interrupted. In this event, please notify Dr. Jabbour.

Treatment should be interrupted for grade 4 or greater dysphagia or odynophagia. Acute esophageal toxicity, which typically can occur within two weeks of the initiation of treatment and manifests as dysphagia, odynophagia, reflux symptoms, etc. should be pharmacologically managed with the following approach and should be initiated at the first signs or symptoms of esophageal toxicity. Recommended treatments are provided in the table below.

Management of Radiation Esophagitis
1) Ketoconazole 200 mg PO q day OR

2) Fluconazole 100 mg PO q day until the completion of radiation

3) Magic mouthwash as per institutional standards

4) Ranitidine 150 mg PO BID (or other H2 blocker or a proton pump inhibitor such as omeprazole) until the completion of radiation

5) Grade 4 esophagitis: hold RT + chemotherapy until grade 2 or less. We expect a significant portion of patients will experience grade 3 esophagitis.

5.5.1.21 Concurrent Chemotherapy Administration

Concurrent Chemotherapy: The doses of chemotherapy to be given **concurrently with conformal radiotherapy** will be paclitaxel (50 mg/m2/wk) and carboplatin (AUC=2/wk). Patients will receive the paclitaxel and carboplatin on the following days of conformal radiotherapy: Days 1, 8, 15, 22, 29, and 36 (+/- 1day due to potential national holidays).

5.5.1.22 Carboplatin dose

Carboplatin dose should be calculated using the Calvert formula [(Total carboplatin dose mg) = (target AUC) x (CrCl + 25)].

The Cr Cl should be calculated using the Cockroft-Gault equation (below) and should not exceed 125 mL/min.:
CrCl (ml/min) = (140-age) (Actual weight in kg) x 0.85 (females only)/72 x serum Creatinine (mg/dl)

Maximum carboplatin dose (mg)=target AUC(mg x mg/mL) x 150 mL/min. Therefore, the maximum carboplatin dose should not exceed target AUC (mg x min/mL) x 150 mL/min, but it may be less.

A measured CrCl from a 24 hour urine collection may also be used.
Note: For subsequent weekly doses, a >10% change in the serum creatinine, based on weekly calculated creatinine clearance, will warrant a recalculation of the carboplatin dose.

5.5.1.23Chemotherapy Administration

All drugs will be administered intravenously by intravenous drip. The paclitaxel will be given over 1 hour with standard premedication consisting of diphenhydramine 25-50 mg, an H2-blocker, and dexamethasone (oral or intravenous is acceptable according to local custom) at least 30 minutes prior to paclitaxel. The carboplatin will be given after the paclitaxel over 30 minutes with standard antiemetics.

The chemotherapy should be delivered prior to the radiation therapy on the day of treatment. If the day of chemotherapy falls on a holiday, chemotherapy should be administered

on the next full working day following the holiday (i.e., if the day 8 dose falls on Labor Day, the next chemotherapy dose would be given the following Tuesday). Doses that are missed during the weekly schedule concurrent with radiation therapy will not be made up but will be documented. If treatment breaks are required for longer than 15 days, protocol treatment should be discontinued. Follow up and data collection will continue as specified in the protocol. Further treatment off protocol is at the discretion of the treating physician.

Concurrent Treatment Summary
Dose Schedule
Paclitaxel 50 mg/m2 Days 1, 8, 15, 22, 29, and 36
Carboplatin AUC=2 Days 1, 8, 15, 22, 29,and 36
Radiation 60 Gy, 5 X per week for 6 weeks Days 1-5, 8-12, 15-19, 22-26, 29-33, 36-40

5.5.1.24 Paclitaxel Formulation

Paclitaxel is commercially available in the US. It is a poorly soluble plant product from the Pacific yew, *Taxus brevifolia*. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water. Vials will be labeled with shelf life. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours.

5.5.1.25 Paclitaxel Preparation

Paclitaxel vials should be stored between 2°-25°C (36°-77°F). A sterile solution concentrate, 6 mg/ml in 5 ml vials (30 mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to clinical use. Paclitaxel for injection must be diluted before administration with 5% dextrose USP, 0.9% sodium chloride USP, or 5% dextrose in Ringer's injection to a final concentration of 0.3 to 1.2 milligrams/milliliter. This solution is stable for 27 hours underambient temperature (25 degrees Celsius) and room lighting (Prod Info Taxol□, *1997)*. Use 5% polyolefin containers due to leaching of diethylhexphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized. Each bag/bottle should be prepared immediately before administration. NOTE: Formation of a small number of fibers in solution has been observed after preparation of paclitaxel (NOTE: acceptable limits established by the USP Particular Matter Test for LVP's). Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: Millex-GV Millipore Products) into the *IV* fluid

pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

5.5.1.26 Paclitaxel Administration

Paclitaxel 50 mg/m2 will be administered over 60 minutes weekly during chemoRT.

5.5.1.27 Paclitaxel Adverse Effects:

- Hematologic: Myelosuppression
- Gastrointestinal: Nausea and vomiting; diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, neutropenic enterocolitis, increased liver function tests (SGOT, SGPT, bilirubin, alkaline phosphatase); hepatic failure, hepatic necrosis
- Heart: Arrhythmias, heart block, ventricular tachycardia, myocardial infarction (MI), bradycardia, atrial arrhythmia, hypotension, hypertension, lightheadedness
- Neurological: Sensory (taste), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy, sensation of flashing lights; blurred vision, scintillating scotoma
- Allergy: Anaphylactoid and urticarial reactions (acute); Stevens-Johnson Syndrome; flushing, rash, pruritus
- Other: Alopecia, fatigue, arthralgia, myopathy, myalgia, infiltration (erythema, induration, tenderness, rarely ulceration); radiation recall reaction.

5.5.1.28 Carboplatin Formulation

Carboplatin is supplied as a sterile lyophilized powder available in a single-dose vial containing 50 mg, 150 mg, and 450 mg of carboplatin for administration by intravenous infusion. Each vial contains equal parts by weight of carboplatin and mannitol.

5.5.1.29 Carboplatin Preparation

Carboplatin is commercially available. Unopened vials of Paraplatin are stable for the life indicated on the package when stored at controlled room temperature and protected from light. Immediately before use, the content of each vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP, according to the following schedule:
Vial Strength Diluent Volume
50 mg in 5 ml
150 mg in 15 ml
450 mg in 45 ml
These dilutions all produce a carboplatin concentration of 10 mg/ml. When prepared as directed, Paraplatin solutions are stable for eight hours at room temperature; since no

antibacterial preservative is contained in the formulation, it is recommended that Paraplatin solutions be discarded eight hours after dilution.

5.5.1.30 Carboplatin Administration

Carboplatin will be administered after paclitaxel as an *IV* infusion over 30 minutes. The dose will be calculated based on the patient's actual body weight at each treatment visit and the AUC (area under curve) dosing. **Note**: For subsequent weekly doses, a >10% change in the serum creatinine, based on weekly calculated creatinine clearance, will warrant a recalculation of the carboplatin dose. The dose of carboplatin is calculated (in mg, not mg/m2) as follows, using the modified Calvert formula based on creatinine clearance: (MAXIMUM CREATINE CLEARANCE ALLOWED WILL BE 125 ml/min)

AUC dose = Target AUC* x (Creatinine clearance + 25)
The *Target AUC for carboplatin treatment is AUC=2 (concurrent therapy) or AUC=6 (consolidation therapy).

The creatinine clearance used to calculate the carboplatin dose will be estimated, based on serum creatinine, using the Cockroft-Gault formula:
For males: CrCl (mL/min) = (140-age) x (weight in kg)/72 x serum creatinine in mg/dL
For females: CrCl (mL/min) =0.85 x (140-age) x (weight in kg)/ 72 x serum creatinine in mg/dL

5.5.1.31 Carboplatin Adverse Events

- Hematologic: Myelosuppression
- Gastrointestinal: Nausea and vomiting; hepatic toxicity; electrolyte imbalance; hypomagnesemia; hypercalcemia
- Neurological: Peripheral neuropathy, ocular changes
- Other: Ototoxicity, myalgia, fatigue, allergic reaction

5.5.1.32 Dose Modifications

Paclitaxel (50 mg/m2) and Carboplatin (AUC-2) intravenously weekly during thoracic radiation for 6 weeks

If dose reduction is required during chemoradiation, no re-escalation is allowed in subsequent chemoradiation cycles.

If paclitaxel and/or carboplatin are held for greater than 2 consecutive weeks, the drugs will be held permanently for the duration of concurrent therapy.

The following dose levels are used for dose modifications during both the concurrent chemoradiation phase. There will be no dose reduction below level -1.

Dose Level	Paclitaxel	Carboplatin
0	50 mg/m2	AUC = 2
-1	40 mg/m2	AUC = 1

Hematologic Toxicity
Dose Modification during Concurrent Chemoradiation:

ANC		Platelet	Carboplatin and Paclitaxel Dose
≥ 1,500/mcl	and	≥ 100,000/mcl	Continue w/ previous dose
< 1,500/mcl	or	< 100,000/mcl	Hold*

*Check weekly and resume therapy at previous dose (no dose reduction) when counts recover to ANC ≥ 1,500 and platelets ≥ 100,000/mcl. If, after 3 weeks of holding drugs ANC < 1,500/mcl or platelet < 100,000/mcl, contact Dr Jabbour.

Febrile neutropenia occurring during chemoradiation will result in a decrease of the carboplatin and paclitaxel dose level by –1. Febrile neutropenia occurring despite dose reduction during chemoradiation will result in discontinuation of carboplatin, but continuation of paclitaxel at the previous dose (-1 dose level). Radiation therapy is held for neutropenia (ANC < 500/mcl); radiation therapy may be restarted when the ANC ≥500/mcl.

☐ Renal Toxicity: There are no dose modifications for renal toxicity. It is not necessary to change the dose of carboplatin unless the calculated dose changes by ≥ 10%.

☐ Neurotoxicity (Peripheral)

Paclitaxel doses should be modified for neurologic toxicity (see below). Serum magnesium and calcium levels should be checked; folate and vitamin B12 levels may need to be evaluated especially in older patients.
Grade 1: Give paclitaxel at full dose.
Grade ≥ 2: Hold paclitaxel until neurotoxicity resolves to ≤ grade 1, then resume with one dose level reduction. Continue treatment with carboplatin. If paclitaxel is held for ≥ 21 days, discontinue paclitaxel, but continue treatment with carboplatin.

☐ Hepatic Toxicity:

Give the following doses for paclitaxel only:

AST		Bilirubin	Paclitaxel
≤2.5x ULN	And	<1.5 mg/dl	Same dose level
2.5-5.0 x ULN	And	<1.5 mg/dl	Decrease 1 dose level
>5x ULN	And	≥1.5 mg/dl	Hold*

*Hold paclitaxel until AST ≤ 5 x ULN and bilirubin < 1.5 mg/dl, then resume treatment at one dose level lower. (Continue treatment with carboplatin. If paclitaxel is held for ≥ 21 days, discontinue paclitaxel therapy (continue treatment with carboplatin).

□ Hypersensitivity to Carboplatin

Grade 1: Slow the infusion until symptoms resolve, then restart the infusion at the initial planned rate.
Grade 2: Stop the infusion. Administer H1 and/or H2 blockers +/- dexamethasone, according to physician discretion/institutional guidelines. Restart carboplatin when symptoms resolve and pretreat before all subsequent doses of carboplatin.
Grade 3 or 4: Patient should be removed from all protocol therapy.

□ Hypersensitivity to Paclitaxel

Grade 1: Slow the infusion until symptoms resolve, then restart the infusion at the initial planned rate.
Grade 2: Stop the infusion. Administer H1 and/or H2 blockers +/- dexamethasone according to physician discretion/institutional guidelines. Restart when symptoms resolve and pretreat before all subsequent doses.
Grade 3 or 4: Discontinue therapy with paclitaxel.

□ All Other Treatment-Related Toxicities that Exceed grade 2: (except alopecia, nausea, vomiting, fatigue and anorexia), hold paclitaxel and carboplatin until the toxicities have resolved to grade 2 or less and resume carboplatin and paclitaxel with one dose level reduction.

If unacceptable toxicities related to paclitaxel or carboplatin occur, and chemotherapy must be discontinued, subjects may continue on this clinical trial as long as radiation therapy is completed.

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:

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

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

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

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

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

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

- **Pneumonitis**:
  - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
  - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
  - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- **Diarrhea/Colitis**:
  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
  - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.

- Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

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

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

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

- Pancreatitis

- For **Grade 2** events, treat with corticosteroids. If patient is asymptomatic with isolated laboratory abnormality, pembrolizumab may continue.
- For Grade 3 events, treat with corticosteroids and continue pembrolizumab as clinically appropriate.
- For **Grade 4** events, treat with systemic corticosteroids and hold pembrolizumab.

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

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

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

Table 5 Infusion Reaction Treatment Guidelines

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

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

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

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

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

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

5.7.3 Use in Pregnancy

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

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

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

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

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression

Note: For unconfirmed radiographic disease progression, please see Section 5.2.2

Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 7.1.2.7.1

- 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 18 doses of pembrolizumab

  Note: 18 dosed of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 18 doses may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.5

- Administrative reasons

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

5.8.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that 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. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the

investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.5.5.

5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

5.10 Clinical Criteria for Early Trial Termination

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

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

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

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart (Table 6)

Trial Period:	Screening Phase		Treatment Phase							End of Treatment	Post-Treatment		
				During Pembrolizumab*									
							To be repeated beyond 8 cycles						
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	CRT Weekly Assessments	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up
Scheduling Window (Days):	-28 days	- 14 days	Days 1-42+10 days	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days +7 days post discon	At 60 days ±7 days and at 90±7 days days and 120±7 days post discon	Every 12 weeks ±14 days
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
Post-study anticancer therapy status													X
Survival Status													X
Adverse Events[13]			X	X			X			X	X	X[12]	X

[redacted] IRB
IRB ID:
Approval Date:
Expiration Date:

Trial Period:	Screening Phase		Treatment Phase							End of Treatment	Post-Treatment		
				During Pembrolizumab*									
							To be repeated beyond 8 cycles						
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	CRT Weekly Assessments	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up
Scheduling Window (Days):	-28 days	- 14 days	Days 1-42+10 days	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days +7 days post discon	At 60 days ±7 days and at 90±7 days days and 120±7 days post discon	Every 12 weeks ±14 days
Physical Examination including Vital Signs and Weight/Height and pulse oximetry both resting and walking		X	X	X			X				X	X	
ECOG Performance Status		X	X	X			X				X	X	
Pembrolizumab			X[8]	X			X						
Pregnancy Test – Urine or Serum β-HCG		X[5]	X[5]										
PT/INR and aPTT		X											
CBC with Differential		X	X[14]	X			X						
Comprehensive Serum Chemistry Panel		X	X[14]	X			X						
Direct Bilirubin (if t.bili>ULN), Mg, Phos, LDH, Uric Acid		X		X			X						

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Measured or calculated creatinine clearance (GFR can also be used in place of serum creatinine or CrCl)		X											
T3, FT4 and TSH		X	X[10]	X			X						
Pulmonary Function Tests	X[1]												
Pathology Report for NSCLC confirmation	X[3]												
CT Chest with contrast (based on renal function)	X[2]					X[7]							X[11]
CT or MRI brain	X[2]												
FDG-PET/CT scan	X[2]												
Progression and Survival													X

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Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	CRT Weekly Assessments	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up
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Mandatory unstained slide submission for PD-L1 Analysis	X[4]												
Correlative Studies Blood Collection			X[6]	X[9]									

CRT=chemoradiation, Each treatment cycle of Pembrolizumab is 21 days.

*Follow this schedule for Second Course Phase (Retreatment Period)

[1]PFTs may be obtained 12 weeks from day 1 of chemoradiation

[2]FDG-PET/CT, CT chest and Brain MRI/Head CT scan may be obtained 42 days before day 1 of chemoradiation