MD Anderson IND Sponsor Cover Sheet

Protocol ID	2015-0856
Protocol Title	Phase I Trial of Adjuvant Pembrolizumab After Radiation Therapy for Lung-Intact Malignant Pleural Mesothelioma
Protocol Phase	I
Protocol Version	23
Version Date	6/7/2022
Protocol PI	Matthew Ning
Department	Radiation Oncology
IND Sponsor	MD Anderson Cancer Center
IND #	132194

1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab after hemithoracic radiation therapy for lung intact mesothelioma
Trial Phase	*I*
Clinical Indication	Curative intent
Trial Type	
Type of control	None
Route of administration	IV
Trial Blinding	None
Treatment Groups	Single arm
Number of trial subjects	24
Estimated enrollment period	12-16 months
Estimated duration of trial	*18-24 months*
Duration of Participation	18-24 months

2.0 TRIAL DESIGN

2.1 Trial Design

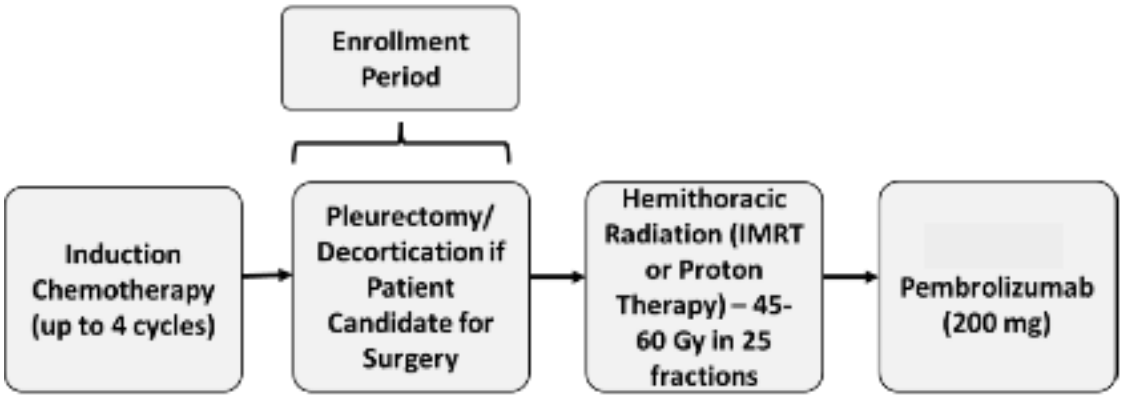
This trial is a single-arm study assessing the role of Pembrolizumab after induction chemotherapy +/- lung-sparing surgery for malignant pleural mesothelioma (MPM). Twelve patients will receive induction chemotherapy with a standard regimen (cisplatin/pemetrexed), followed by surgical resection if feasible with a lung-sparing approach (extrapleural pneumonectomy excluded), followed by hemithoracic radiation therapy with intensity modulated radiation therapy (IMRT) or proton beam therapy (PBT) to a total dose of 45 Gy in 25 fractions to the entire hemithorax, with an optional simultaneous integrated boost of 60 Gy in 25 fractions. Patients then will receive Pembrolizumab, 200 mg every 3 weeks until one of three timepoints (whatever comes first): 1) progression, 2) unacceptable toxicity, 3) 2 years.

In addition, we will enroll 12 additional patients with MPM who receive radiation for palliative reasons to a limited field (non-hemithoracic). This latter group of patients will be enrolled so that the abscopal/systemic effect can be evaluated in the context of very limited treatment options, to include patients that are not candidates for extensive radiation therapy.

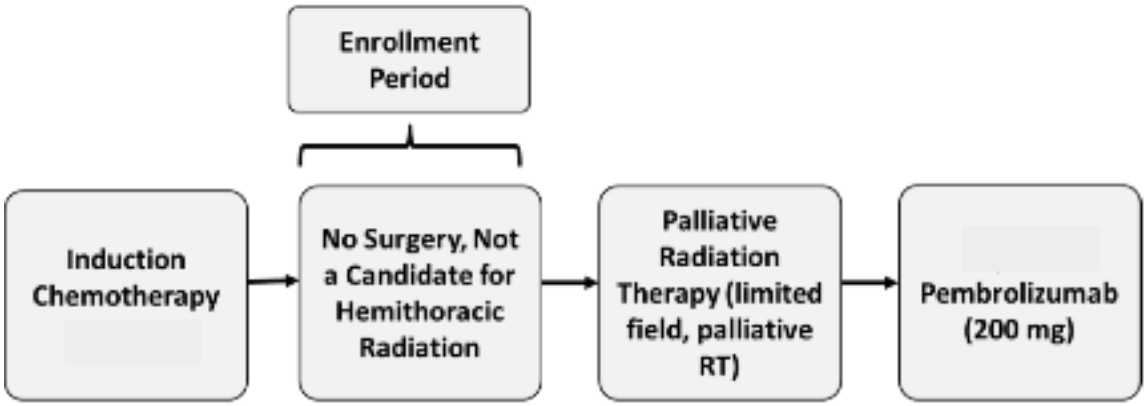
These two independent cohorts of 12 patients will be accrued simultaneously but monitored separately, as outlined in the Statistical Methods section below.

2.2 Trial Diagram

Cohort 1. Patients with Lung Intact to Receive Hemithoracic Radiation Therapy for Definitive Intent



Cohort 2. Patients with Lung Intact to Receive Limited Field, Palliative Radiation Therapy



3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** To determine the safety and tolerability of pembrolizumab administered after radiation therapy in patients with MPM who have not undergone extrapleural pneumonectomy. Two cohorts will be included, one receiving extensive hemithoracic radiation and the other receiving more limited, palliative treatment. These cohorts will be accrued simultaneously but monitored separately for toxicity.

Hypothesis: Pembrolizumab will be well tolerated when given after radiation therapy for MPM.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: To assess progression-free and overall survival (PFS and OS, respectively) in patients receiving Pembrolizumab after radiation therapy for MPM.

Hypothesis: Adding Pembrolizumab to radiation therapy for MPM will improve PFS and OS compared to historical controls.

3.3 Exploratory Objective

(1) **Objective:** To evaluate biomarkers of interest, including cytokines, measurements of T-cell activation, and serum exosome microRNAs with the delivery of Pembrolizumab after radiation therapy for MPM.

4.0 BACKGROUND & RATIONALE

4.1 Background

Malignant pleural mesothelioma (MPM) occurs in approximately 2000-3000 new individuals each year in the United States.[1] MPM remains a difficult disease to treat with median overall survival rates remaining between 9–17 months, regardless of stage.[2-4] In patients that present with locoregionally confined disease (e.g. non-metastatic), the standard of care for definitive intent has historically involved induction chemotherapy followed by an extrapleural pneumonectomy (EPP=removal of the ipsilateral lung, pleura, diaphragm, and pericardium) and consideration of postoperative radiation therapy. However, many patients cannot tolerate an EPP, and as a result this resection is not a viable option for a large percentage of patients. In addition, several recent clinical studies have concluded that an EPP does not provide a survival advantage over lung sparing approaches, including a pleurectomy/decortication (e.g. "stripping" of the pleura without removing the lungs) or no surgery.

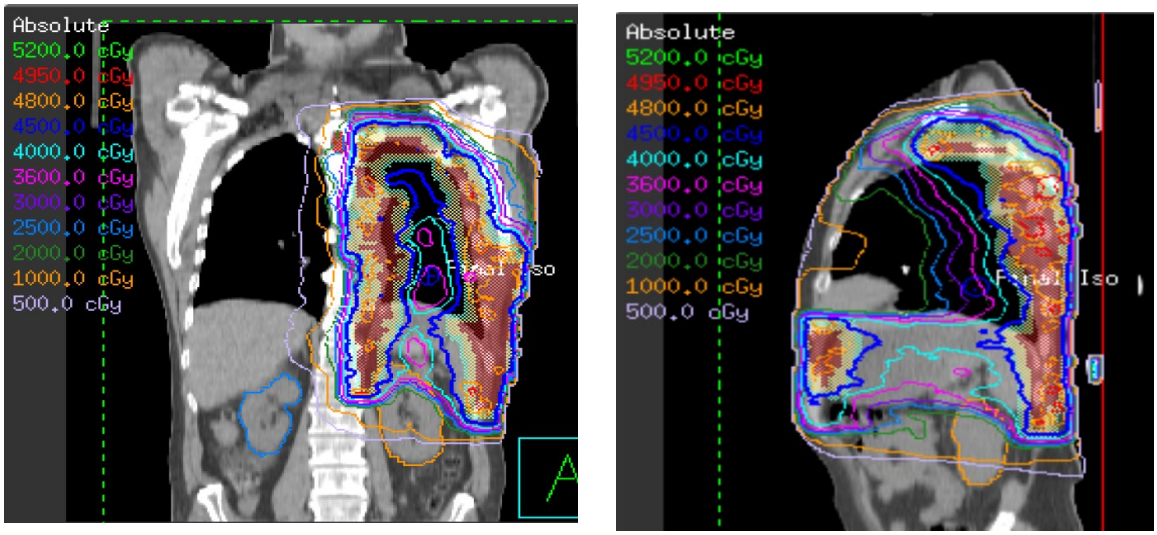
Specifically, The Mesothelioma and Radical Surgery trial (MARs)[5, 6] which compared 50 randomized MPM patients to EPP (n=24) versus "no EPP" (n=26) reported that receipt of EPP led to a worse survival (hazard ratio (HR) 1.90, 95% CI 0.92 – 3.93, p=0.082). In this study, only 16 of the 24 patients in the EPP arm actually received the EPP and 19% (n=3) had post-operative deaths. After accounting for prognostic factors (stage, histology, gender, age), the HR for EPP was reported as 2.75 (p=0.016). The median overall survival was 14.4 months for patients in the EPP arm compared to 19.5 months for the patients in the "no EPP" arm. This trial, although limited in numbers of patients, suggested that at worst, EPP can harm patients and at best, there was no clinical benefit for MPM patients. In addition, Lang-Lazdunski et al.[7] conducted a nonrandomized study of consecutive MPM patients and compared 25 who received neoadjuvant chemotherapy followed by EPP and radiation to 54 patients with P/D, hyperthermic lavage, adjuvant radiation and chemotherapy. The study reported that the P/D arm was superior to the EPP arm for compliance, toxicity and survival. Patients in the P/D arm had 100% compliance to complete trimodality treatment versus 68%

in the EPP arm. The P/D arm also had a higher median overall survival of 23 months versus 12.8 months.[7]

Studies such as these have suggested that patients are optimally treated with lung sparing approaches. However, radiation therapy when the ipsilateral lung is intact, with or without surgery, presents unique issues. First, the presence of functional lung tissue on the same side as the target volume exposes the patient to the risk of radiation pneumonitis in this lung. Second, presuming that the ipsilateral lung is functional, patients can theoretically experience significant functional decline due to the difficulty in sparing this structure. Finally, if much of the ipsilateral lung is nonfunctional after RT, a "shunting" effect can occur whereby patients continue to perfuse to the ipsilateral lung, yet air exchange does not occur. For these reasons, hemithoracic radiation treatment with two functional lungs can paradoxically be more challenging than with only one lung intact.

However, a limited number of institutions, including ours, have utilized advanced techniques to treat patients that do not undergo EPP with hemithoracic radiation therapy in the definitive setting. The first of these approaches is IMRT, and **Figure 1** depicts a representative IMRT plan in this setting. We have recently published our results of 22 patients who underwent P/D followed by adjuvant IMRT to the involved hemithorax. Patients were treated to 45 Gy in 25 fractions with 9 patients receiving a simultaneous boost to 60 Gy to high risk areas. Twenty patients received chemotherapy (15=induction, 2=adjuvant, 3=both). Median follow up was 14.7 months after surgery (range 4.1-37.1 months). The therapy was well tolerated. No grade 4-5 pulmonary toxicity was noted. One case of grade 4 thrombocytopenia was observed. Progressive decreases in pulmonary function were noted after surgery and IMRT. Median baseline % predicted FVC, FEV1, and DLCO were 90%, 84%, and 87%. The change in % predicted FVC, FEV1 and DLCO was -18%, -11% and-17% after surgery and -25% (p=0.02), -18% (p=0.01), and -27% (p=0.01) after IMRT. Rates of overall survival and progression free survival were 73% and 60% at 1 year, respectively, and 52% and 32% at 2 years, respectively. Outcomes for IMRT after P/D were compared to 22 matched patients who underwent IMRT after EPP. The patients who underwent P/D had less grade 4-5 toxicity (0/22 vs 3/22, p=0.23) and a trend towards improved median overall survival (28.4 vs 14.2 months, p=0.14), median disease free survival (15.4 vs 10.2 months, p=0.18), and median time to distant metastasis (not reached vs 11.8 months, p=0.15). [8] Thus, these results suggested that hemithoracic radiation after P/D provides comparable toxicity and efficacy as after EPP.

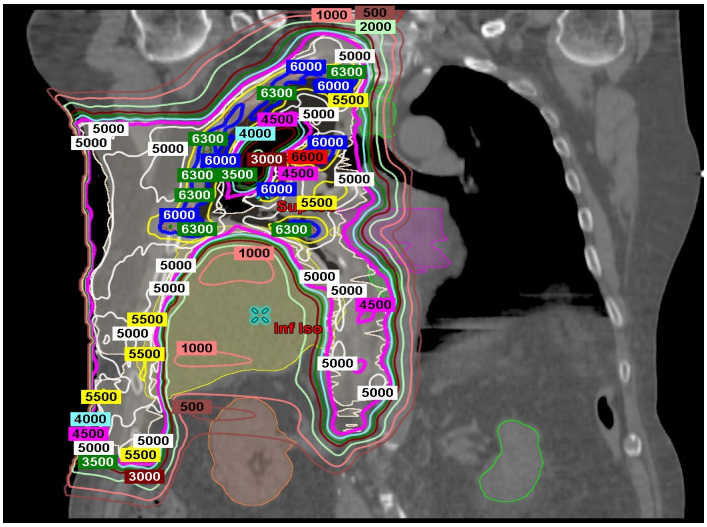
Figure 1. IMRT treatment plan with the lung intact.



Indeed, other reports have also been consistent with these findings. Between 2005 and 2010, 36 patients from Memorial Sloan-Kettering Cancer Center (MSKCC) with malignant pleural mesothelioma who were unable to undergo pneumonectomy underwent induction chemotherapy (89% of patients) and then P/D with adjuvant IMRT (56%) or IMRT with biopsy only (44%). All patients were treated to the pleural surface of the involved hemithorax to a median dose of 46.8 Gy. Seven (20%) patients developed high grade pneumonitis (including 1 death). For patients who underwent PL/D prior to IMRT, the 1- and 2-year survival rate was 75% and 53%, and the median survival was 26 months. For patients who did not undergo surgical resection, the 1- and 2-year survival rate and median survival trended lower at 69% and 28%, and 17 months respectively.[9] These investigators also recently examined patterns of failure when treating the external pleural hemithorax in 67 patients to a similar volume as Figure 2. The rate of in-field local failure was 64%, with 1- and 2-year total failure rates of 56% and 74%, respectively. Interestingly, the authors also found that failure within the fissures was 16%, and only 1 patient had an incisional failure despite the practice of not routinely boosting the incisional sites [10]. Based on these two trials, we have recently completed a prospective study in conjunction with MSKCC examining the efficacy of patients treated with induction chemotherapy, then P/D or no surgery, followed by hemithoracic radiation therapy with IMRT. Thirty nine patients enrolled, and in an interim report 21 patients completed IMRT. Only one patient experienced Grade 3 pneumonitis, a rate below that which is often reported for locally advanced non-small cell lung cancer (NSCLC).[11]

A second radiation technique that can be used to further increase normal tissue sparing is PBT, specifically intensity modulated proton therapy (IMPT). Proton particles provide a dose distribution advantage by delivering less dose proximal and distal to the target region, with a sharper dose falloff (known as the “Bragg Peak”). IMPT has been studied in multiple malignancies, including NSCLC [12-14]. In addition, we have recently reported our early experience with IMPT for lung-intact malignant pleural mesothelioma, in which we found lower does to multiple structures, including the contralateral lung, heart, and esophagus. As a result, we continue to treat select patients with this technique [15]. **Figure 2** shows an IMPT plan in a patient with the ipsilateral lung intact.

Figure 1. Proton beam therapy (IMPT) treatment plan with the lung intact.



In this study, we assess the role of conformal radiation techniques as part of a lung-sparing regimen with immunotherapy in patients with malignant pleural mesothelioma. Specifically, we are combining radiation therapy with Pembrolizumab, and we ***hypothesize that through the utilization of inhibitors of the PD1/PDL1 axis after radiation therapy in MPM, we will improve rates of both local and distant disease control by taking advantage of the complementary biologic effects of the two modalities.***

Note that in addition to enrolling 12 patients with MPM who will receive induction chemotherapy and hemithoracic radiation therapy, we will also enroll 12 additional patients who will receive palliative radiation therapy to a limited field (non-hemithoracic), to assess the safety/efficacy of this approach. In particular, this cohort of patients will allow us to assess the abscopal/systemic effect that has been observed in patients receiving radiation therapy and immunotherapy outside of the radiation field. We will also be able to assess outcomes in the context of delivering less aggressive radiation fields. Indeed, it may be the case that when immunotherapeutic agents are delivered, more limited fields can be used to provide analogous rates of disease control as in a hemithoracic field, but with more limited toxicity. We will be able to accrue to these two arms concurrently, which will also increase accrual rates and with one trial break for toxicity assessment halfway through each arm.

There is evidence for the immune checkpoint process playing an active role in MPM. Both the T-cell inflamed phenotype and PD-L1 expression have been observed in this malignancey, particularly in non-epithelioid tumors. In addition, PD-L1 expression is associated with a poorer prognosis [16]. And recently, results from the KEYNOTE-028 trial were presented at the American Association for Cancer Research annual meeting. Investigators enrolled 25 patients with MPM and PD-L1 positive disease who were then treated with Pembrolizumab for 24 months or until progression/intolerable toxicity. They observed a 28% objective response rate and a 76% disease control rate that was better than the historical response for second-line chemotherapy. As a result, these findings were encouraging for

further evaluation of this agent in MPM. The current study would be the first of its kind to combine Pembrolizumab with radiation therapy.[17]

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

Please see section 4.1 for a detailed description of the rationale for this this trial. We will enroll patients with malignant pleural mesothelioma who do not undergo an EPP, the rationale being that these patients often have a worse prognosis, with limited treatment options. Therefore, we are aiming to benefit these patients using our highly conformal radiation techniques in combination with Pembrolizumab.

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 Pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of Pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 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 Pembrolizumab program has shown that a lower dose of Pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for Pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e.

5-fold higher dose and exposure). 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 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 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

Given the lack of experience combining radiation therapy for MPM and immunotherapy, the primary endpoint will be high-grade toxicity, defined specifically in Table 3 below. Specifically, the Off-Study Criteria defined in Table 3 are the “Unacceptable” high-grade toxicities in the trial. That is, patients that meet these criteria will be considered as having met the study endpoint and will be taken off study. Patients will be monitored for 4 months after the start of RT. Since RT is approximately 1 month in duration, this monitoring period will include 3 months after the end of RT.

4.2.3.1 Efficacy Endpoints

Our secondary endpoints will be to estimate progression free survival (PFS) and overall survival (OS).

4.2.3.2 Biomarker Research

We will assess multiple biomarkers of interest through the collection of blood and tissue specimens through the following optional studies:

A) Tissue specimen collection for biomarker analysis: Diagnostic and surgically resected tumor tissue will be acquired from the source used to establish the diagnosis of malignancy, including archival specimens stored in the Pathology Department and

residual fresh or fixed tissues banked in institutional tissue banks. Cytologic samples may also be included, though cell blocks are strongly preferred. The cell and tissue samples will be catalogued, then reviewed by a pathologist for malignant cell content and pathological analyses, and for correlative marker studies. The molecular marker analysis will include, among others, the analysis of protein expression, gene expression, copy number, mutations, and translocations, and micro-RNA expression abnormalities. The methodology to be used to examine molecular changes will be selected based on the characteristics of the sample collected (e.g. cells or tissue, archival or frozen). Immune markers of interest include but are not limited to the following:

Inhibitory Markers (blocking T-cell activation): PD-1, PD-L1, CTLA-4, BTLA, TIM3, LAG3

Costimulatory Markers (promoting T-cell activation): CD28, CD80, CD86, HLA-1, ICOS, ICOSL, 41BBL, 41BB

B) Serologies/Blood-Based Biomarkers – For evaluation of circulating immune biomarkers of interest including cytokines, measurements of T-cell activation, circulating tumor DNA (ctDNA) and exosome microRNAs. Three categories of specimens will be collected:

A) EDTA Vaccutainer (CAFs): 10 mL = 1 x 10 mL

B) Streck CF-DNA BCT (ctDNA): 10 ml = 1 x 10 mL

C) Sodium Heparin (immunoprofiling=immuno): 60 ml = 6 x 10 mL

All blood will be collected and processed by Thoracic Research Team according the institutional and laboratory standard operating procedures (SOPs).

Optional blood samples will be collected at the following timepoints:

1) Prior to RT (baseline): ctDNA, cytokine angiogenic factors (CAFs), immunoprofiling

2) After RT (+/- 3 days): CAF, immunoprofiling

3) After 2 cycles of immunotherapy (+/- 3 days): CAF, immunoprofiling

4) Progression/off study within 30 days of discontinuation or prior to starting next treatment: ctDNA, CAF, immunoprofiling methodology

4.3 Entry Criteria

4.3.1 Diagnosis/Condition for Entry into the Trial

Patients will have a diagnosis of malignant pleural mesothelioma and will not have undergone EPP as a component of their treatment.

4.3.2 Subject Inclusion Criteria

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

1. Patients must have a histologic diagnosis of malignant pleural mesothelioma, with histologic diagnosis from the pleura or relevant lymph node stations, including mediastinal, hilar, or supraclavicular lymph nodes.

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

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

4. Have measurable or non-measurable disease per RECIST 1.1. However, note that patients in Cohort 1 that have undergone an R0 resection will be eligible for the trial.

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

6. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10-15 days of treatment initiation.

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.	

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

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

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

Additional Inclusion Criteria – Cohort 1 (Patients Receiving Hemithoracic Radiation Therapy)

1. Patients must not have evidence of metastatic disease per PET/CT scan. Mediastinal lymph node involvement is acceptable.

2. Patients will have received at least 2 cycles of induction chemotherapy with pemetrexed/cisplatin or pemetrexed/carboplatin.

3. The following pulmonary function tests are required:

    a. $FEV_1 \geq 30\%$ of predicted postoperative (ppoFEV1, as if the patient underwent a pneumonectomy) based on the following formula using a quantitative perfusion scan: Predicted post-resection $FEV_1 = FEV_1$ x % perfusion to the uninvolved lung from the quantitative perfusion report.

    b. DLCO>35% predicted.

4. Patients must be assessed to be a suitable candidate for hemithoracic radiation therapy per the treating radiation oncologist. If the patient undergoes pleurectomy/decortication, they must initiate hemithoracic radiation therapy within 4 months of the surgery date. Patients that do not meet the dose constraints outlined below will be removed from the study prior to radiation therapy.

Additional Inclusion Criteria – Cohort 2

1. Patients must be assessed to be a suitable candidate for radiation therapy by the treating radiation oncologist. Patients that do not meet the dose constraints outlined below will be removed from the study prior to radiation therapy.

2. Any prior number of prior therapies, including prior immunotherapy, is allowed.

3. Patient has received prior treatment with a platinum-pemetrexed regimen.

4.3.3 Subject Exclusion Criteria

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

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

2. Has a diagnosis of immunodeficiency. Note that patients should not receive steroids during Pembrolizumab administration.

3. 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 and who have not recovered adequately from this treatment (≤Grade 2 toxicity at the time of enrollment).

7. Has a known additional malignancy that is progressing or requires active treatment. Patients with a stage I-III cancer that has been cured over two years ago are *not* excluded in the study.

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

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

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

11. Has an active infection requiring systemic therapy.

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

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

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

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

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

17. Evidence of interstitial lung disease.

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

Additional Exclusion Criteria – Cohorts 1

1. Patients undergoing an EPP. Lung sparing surgeries, such as pleurectomy/decortication, are acceptable.

Additional Exclusion Criteria – Cohort 1

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

Additional Exclusion Criteria – Cohort 2

1. Patients in which hemithoracic radiation therapy is planned.

2. Patients who have received EPP for mesothelioma.

Additional Exclusion Criteria – Cohorts 1 and 2

1. Patients with inherited syndromes associated with hypersensitivity to ionizing radiation, specifically **patients with known history of** Ataxia-Telengiectasia, Nijmegen breakage syndrome.

4.4 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 X mg/kg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
Note: Patients must initiate treatment with Pembrolizumab within 1 month of the last day of radiation therapy.					

4.4.1 Dose Selection/Modification

4.4.1.1 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 are provided in the Pharmacy Manual.

4.4.1.2 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 Guidelines for Drug-Related Adverse Events (Note that discontinuation of subjects for all toxicities in Table 3 are contingent on the conclusion that they are treatment related.)

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject/Off-Study Criteria ("Unacceptable" Toxicities)
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue/Off-Study
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exceptions below)[1,2]	Permanently discontinue/Off-Study
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue/Off-Study
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue/Off-Study
Hypothyroidism	2-4	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue/Off-Study
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks. Recurrent grade 2 pneumonitis requires discontinuation of pembrolizumab.
	3-4	Permanently discontinue	Permanently discontinue/Off-Study
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue/Off-Study
All Other Drug-Related Toxicity[3]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue/Off-Study
All other Radiation-Related Toxicity by CTCAE v4.0 criteria (cardiac, esophageal, pericarditis, bowel, etc)	3 or greater	Off Study	Off Study

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

[1] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[2] For patients with Grade 3 transaminitis, will recheck liver enzymes in 1-2 weeks and if the toxicity changes to Grade ≤2, patients can remain on study.

[3] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

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

Management of Radiation Pneumonitis

Patients who develop Grade ≥2 pneumonitis will be managed according to standard clinical guidelines. If supportive measures are unsuccessful, and/or if the symptoms persist despite this approach, steroids and a referral to pulmonary medicine will be considered. A standard regimen of prednisone includes 40-60 mg daily x 2 weeks, then tapering over the next 3-6 weeks based on symptom status. Interventions such as hospitalization, intravenous steroids, and oxygen administration will be performed at the treating physician's discretion.

As noted in the Statistical Considerations section below (Section 8.0), the study will be stopped if 3/6 or 6/12 patients develop Grade 3 or higher radiation pneumonitis. If 0/6, 1/6, or 2/6 patients develop this toxicity, the study will continue. No dose de-escalation will be performed because all patients are already receiving the minimal therapeutic microscopic dose of radiation, and therefore any further reductions in treatment intensity are not likely to control the disease (and still carry the risk of toxicity). Furthermore, our institution does not have experience escalating the radiation dose in mesothelioma higher than that described in this study, and thus it is not appropriate to do so in conjunction with Pembrolizumab without first assessing the effect of higher doses of radiation therapy alone (without immunotherapy). The study is thus addressing the question of whether our institution's current radiation regimen for malignant pleural mesothelioma, in both the unresectable and pleurectomy/decortication settings, is safe with Pembrolizumab. In essence, the two regimens that we are testing are those in the two cohorts that we have included, the first being the most aggressive and including the entire hemithorax (Cohort 1), and the second being a much more limited field and including only the region of palliation (Cohort 2). This trial will provide data as to whether the immunotherapy-radiation combination should be further explored in neither context, only the less aggressive scenario, or in both patient populations.

4.4.2 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 at MDACC.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks for up to 2 years

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.

4.4.3 Trial Blinding/Masking

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

4.4.4 Radiation Therapy

4.4.4.1 Suggested Simulation Procedure

Prior to radiation, we suggest that patients undergo a renal scan and baseline creatinine, to assess potential toxicity to the ipsilateral kidney. Patients will undergo CT simulation in the Department of Radiation oncology. Immobilization will occur with a vac-loc cradle and the arms above the head. 4D CT images will be obtained to assess for respiratory motion, and will scan from the lung apex to approximately L2 inferiorly. Wiring the scars and drain sites with bolus is optional. If bolus is used, we suggest 0.5 cm thickness and 3.5 cm in diameter. Treatment will be planned using IMRT or IMPT and delivered with image-guided radiation therapy (IGRT).

4.4.4.2 Suggested Target Delineation

Cohort 1 – Hemithoracic Radiation Therapy

For patients with no gross residual disease, above the level of the diaphragm the planning target volume (PTV) will encompass the ipsilateral external pleura using a "rind" volume, including an 8 mm inner margin (PTV_inner) and 1-1.5 cm outer margin (PTV_outer). The outer margin will should be extended lateral to the ribs, with approximately a 0.5 cm margin. Non-enhancing nodal beds will not be contoured or treated. Below the level of the diaphragm, the PTV will encompass only a single crescent-shaped contour with will be named the PTV_outer. If bolus is placed, the target volume should extend towards the surface and encompass the region of the bolus.

Cohort 2 – Non-Hemithoracic Radiation Therapy

The gross disease, as delineated on the PET/CT scan and/or the CT scan with contrast, will be contoured as the GTV. A 0.5-1 cm margin will be defined as the CTV, and another 0.5 cm margin will be placed as the PTV if daily kV imaging is performed.

4.4.4.3 Treatment Planning and Prescription Dose

Cohort 1 – Hemithoracic Radiation Therapy

Patients will be prescribed a prescription dose of 45 Gy in 25 fractions to the PTV, and 2.4 Gy x 25 fractions to the GTV (if applicable) using a simultaneous integrated boost. Either IMRT or IMPT will be utilized, using techniques described in prior publications from our institutions [15, 18].

Cohort 2 – Non-Hemithoracic Radiation Therapy

Patients will be treated to one of the following prescribed doses: a) 3 Gy x 10 fractions = 30 Gy, b) 4 Gy x 5 fractions = 20 Gy, c) 5 Gy x 5 fractions = 25 Gy, or d) 45-52.5 Gy in 15 fractions. Patients will be treated using either IMRT or 3D conformal therapy.

4.4.4.4 – Radiation Dose Constraints – Both Cohorts

Required Dose Constraints – Patients are required to meet the following dose constraints: 1) Normal Tissue Complication Probability (NTCP) of the lung <25%, calculated with the Lyman-Kutcher-Berman model [19]. 2) At least 93% of the contralateral lung must receive less than 20 Gy (V20<7%). 3) Maximum spinal cord dose of <50 Gy.

Suggested Dose Constraints – We suggest the following dose constraints: 1) At least 50% of heart receive less than 30 Gy, 2) At least 50% of the liver receive less than 30 Gy. 3) Mean dose to stomach (not PTV) <30 Gy, 4) Maximum bowel dose<55 Gy, 5) Kidney V18≤50%.

4.5 Randomization or Treatment Allocation

No randomization will be performed.

4.6 Stratification

No stratification will be done.

4.7 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.

4.7.1 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.

4.7.2 Prohibited Concomitant Medications

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

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

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.

4.8 Rescue Medications & Supportive Care

4.8.1 Supportive Care Guidelines

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

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

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

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

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

    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.

- For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

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

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

- **Hypophysitis**:

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

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

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid

taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

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

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

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

Table 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	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.**	
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

4.9 Diet/Activity/Other Considerations

4.9.1 Diet

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

4.9.2 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.

4.9.3 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.

4.9.4 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.

4.10 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: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if meeting the following criteria: 1) clinically stable, or 2) clinically improved, at the physician's discretion.
- 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 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.

  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months 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.

4.10.1 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.

4.11 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.

5.0 TRIAL FLOW CHART

5.1 Study Flow Chart

Trial Period:	**Screening Phase**		**Treatment Cycles**								**End of Study Treatment**	**Post-Study Treatment**	
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2, Pre-RT)	Last Week of RT	1	2	3	To be repeated beyond 7 cycles 4	5	6	7	Discon	Safety Follow-up	Follow Up Visits Every 6 weeks (42 +/- 7 days) until to 48 weeks, then every 12 weeks (+/- 7 days) to 5 years
Scheduling Window (Days):		**-45 to -1**	± 7	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	Approxima-tely 30 days post discon	
Administrative Procedures													
Pre-screening Consent	X												
Inclusion/Exclusion Criteria	X	X											
Demographics, Medical History, and Disease History		X											
Prior and Concomitant Medication Review		X	X	X	X	X	X	X	X	X	X	X	X
Pembrolizumab Administration				X	X	X	X	X	X	X			
Post-study anticancer therapy status											X	X	X
Survival Status			X	X	X	X	X	X	X	X	X		X
Clinical Procedures/Assessments													
Review Adverse Events			X (start of RT: Grade 3 or higher)	X (begin-ning Pemb-ro: all toxici-ties)	X	X	X	X	X	X	X	X	X
Full Physical Examination		X											
Directed Physical Examination			X	X	X	X	X	X	X	X	X	X	X
Vital Signs and Weight		X	X	X	X	X	X	X	X	X	X	X	X

Trial Period:	**Screening Phase**		**Treatment Cycles**								**End of Study Treatment**	**Post-Study Treatment**	
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2, Pre-RT)	Last Week of RT	1	2	3	To be repeated beyond 7 cycles 4	5	6	7	Discon	Safety Follow-up	Follow Up Visits Every 6 weeks (42 +/- 7 days) until to 48 weeks, then every 12 weeks (+/- 7 days) to 5 years
Scheduling Window (Days):		**-45 to -1**	± 7	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	Approxima-tely 30 days post discon	
ECOG Performance Status		X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory													
Pregnancy Test – Urine or Serum β-HCG		X											
Use of Birth Control		X											
PT/INR and aPTT		X											
CBC with Differential		X		X	X	X	X	X	X	X	X		
Comprehensive Serum Chemistry Panel		X		X	X	X	X	X	X	X	X		
Urinalysis		X											
T3, FT4 and TSH		X		X	X	X	X	X	X	X			
Pulmonary Function Tests		X								X (q6 cycles)	X		X
Quantitative Perfusion Scan (Cohort 1)		X[1]											
Renal Perfusion Scan (Cohort 1)		X[1]											
Efficacy Measurements													
Tumor Imaging		X					X			X – repeat every 3 cycles			X
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood (Optional)													
Archival or Newly Obtained Tissue Collection		X											
Correlative Studies Blood Collection (as described in section 4.2.3.2)		X (ctDNA,	X (CAF,			X (CAF,					X (ctDNA, CAF, immuno)		

Trial Period:	**Screening Phase**		**Treatment Cycles**								**End of Study Treatment**	**Post-Study Treatment**	
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2, Pre-RT)	Last Week of RT	1	2	3	To be repeated beyond 7 cycles 4	5	6	7	Discon	Safety Follow-up	Follow Up Visits Every 6 weeks (42 +/- 7 days) until to 48 weeks, then every 12 weeks (+/- 7 days) to 5 years
Scheduling Window (Days):		**-45 to -1**	± 7	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	Approxima-tely 30 days post discon	
		CAF, immuno)	immuno)			immuno)							

NOTE: All screening studies should be done within 45 days of radiation therapy. The exception to this guideline is laboratory tests, which should be done within 15 days of radiation therapy.

[1]Patients only need a quantitative perfusion scan and a renal scan if they enroll on cohort 1.

6.0 TRIAL PROCEDURES

6.1 Trial Procedures

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

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

6.1.1 Administrative Procedures

6.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

6.1.1.2 Inclusion/Exclusion Criteria

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

6.1.1.3 Medical History

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

6.1.1.4 Prior and Concomitant Medications Review

6.1.1.4.1 Prior Medications

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

6.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

6.1.1.5 Disease Details and Treatments

6.1.1.5.1 Disease Details

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

6.1.1.5.2 Prior Treatment Details

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

6.1.1.5.3 Subsequent Anti-Cancer Therapy Status

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

6.1.2 Clinical Procedures/Assessments

6.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs. Adverse events will be recorded in the Prometheus database. We will capture all adverse events (related to radiation therapy, pembrolizumab, or a combination of the two). AE's will be collected weekly during radiation therapy and grade 3 or higher toxicities will be documented. The PI or designee will be responsible for determining attribution for all events, which will also be documented in the Prometheus database.

6.1.2.2 Full Physical Exam

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

6.1.2.3 Directed Physical Exam

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

6.1.2.4 Vital Signs

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

6.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

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

6.1.2.6 Tumor Imaging and Assessment of Disease

Patients will have their history collected at screening, and a physical exam will be performed at screening, post-RT (+/- 7 days), on day 1 of each pembrolizumab cycle, at the end of treatment visit, and post-treatment. Patients will be imaged with either: 1) CT scan of the chest with contrast, or 2) PET/CT scan. This imaging will be done with the following frequency: prior to radiation therapy, after cycle 3 of pembrolizumab, and every 3 cycles thereafter. Pulmonary function tests will be done at the following timepoints: 1) At enrollment, 2) after every 6 cycles of pembrolizumab, and 3) at the discontinuation of treatment.

6.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

Tissue and tumor collection will be performed at diagnosis and at surgical resection or rebiopsy, as described in Section 4.2.3 above.

6.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below.

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

Table 5 Laboratory Tests

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

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

‡ If considered standard of care in your region.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 45 days prior to the first dose of treatment. All screening studies should be done within 45 days of radiation therapy. The exception to this guideline is laboratory tests, which should be done within 15 days of radiation therapy. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

6.1.3.1 Pharmacokinetic/Pharmacodynamic Evaluations

6.1.3.1.1 Blood Collection for Serum Pembrolizumab

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

6.1.3.1.2 Blood Collection for Anti-Pembrolizumab Antibodies

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

6.1.4 Other Procedures

6.1.4.1 Withdrawal/Discontinuation

Off-Study Criteria. Patients will remain on study until completion until they: 1) experience a Grade 3 or higher toxicity during radiation therapy (in which case they will be deemed to be non-evaluable), 2) meet the criteria of Permanent Discontinuation/Off-Study Criteria outlined in Table 3 above (evaluable patient), in which case subjects will be followed until **resolution of symptoms,** 3) are lost-to follow-up, 4) elect to come off study, or 5) die.

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.5. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

If a patient comes off study for toxicity, follow-up will still occur through the research team +/- clinical staff for survival purposes, either through clinic visits as clinically warranted or direct patient calls if the patient no longer follows up at our institution.

6.1.4.2 Blinding/Unblinding

6.1.5 Visit Requirements

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

6.1.5.1 Screening

6.1.5.1.1 Screening Period

Patients will be screened with the appropriate tests prior to entering the study.

6.1.5.2 Treatment Period

The treatment period will encompass both the radiation therapy and the Pembrolizumab, administered as described above. Patients will undergo assessment of disease status

6.1.5.3 Post-Treatment Visits

7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab (as described in Section 7.1.5.5) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

6.1.5.4 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 6 weeks (42 ± 7 days) by radiologic imaging to monitor disease status. After 48 weeks the imaging time point will occur every 12 weeks (± 7 days), up to 5 years. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section 7.1.5.5. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 7.1.5.5 will move from the follow-up phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.2 – Trial Flow Chart for Retreatment.

6.1.5.4.1 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.1.5.5 Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab with SD or better may be eligible for up to one year of additional pembrolizumab therapy if they progress within one year after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- **Either**
  - Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1, and
    - Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy
    - Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

      OR
  - Had SD, PR or CR and stopped pembrolizumab treatment after 24 months of study therapy for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 5.1.2

- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.

- Female subject 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 child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.

- Male subject 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.

- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might 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.

- Absence of rapid progression of disease

- Absence of progressive tumor at critical anatomical sites (e.g. cord compression) requiring urgent alternative medical intervention.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab. Treatment will be administered for up to one additional year.

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

6.2 Assessing and Recording Adverse Events

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

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

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

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

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

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

In addition to documenting all Grade 3 or higher toxicities during radiation therapy, all adverse events will be recorded from the time of study invervention (pembrolizumab) through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1.

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

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

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

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

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

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

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

6.2.3.1 Serious Adverse Events

Serious Adverse Event Reporting (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.**

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- **Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.**

- **Serious adverse events will be captured from the time of the first protocol-specific intervention, until 90 days after the last study treatment/intervention, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**

- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.**

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Investigator Communication with Supporting Companies:

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time of first protocol intervention through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. The MD Anderson Internal SAE Report Form for Prompt Reporting will be used, with the Merck protocol number referenced (3475-360).

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

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

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

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

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

6.2.3.2 Events of Clinical Interest

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

1. an overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

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

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

1. Additional adverse events:

   A separate guidance document has been provided entitled “Event of Clinical Interest Guidance Document” (previously entitled, “Event of Clinical Interest and Immune-Related Adverse Event Guidance Document”). This document can be found in Appendix 4 and provides guidance regarding identification, evaluation and management of ECIs and irAEs.

   ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn:

Worldwide Product Safety; FAX 215 993-1220), regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

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

6.2.4 Evaluating Adverse Events

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

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

Table 6 Evaluating Adverse Events

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

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

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

6.2.5 Sponsor Responsibility for Reporting Adverse Events

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

7.0 STATISTICAL ANALYSIS PLAN

7.1 Statistical Analysis Plan Summary

Our Phase I study, consisting of two distinct cohorts of patient, will assess toxicity of two radiation treatment plans. Patients will be assigned to one of two study cohorts based on eligibility characteristics. Randomization is not possible due to the distinct criteria required for the administration of the radiation treatment plan. Each study cohort will be monitored for toxicity independently using a single treatment plan.

7.2 Statistical Analysis Plan

We will enroll a total of 24 patients, twelve patients to each cohort consisting of distinct radiation and immunotherapy treatment plans. For each study cohort, treatment-related toxicity is defined in Table 3 above (in the column "Discontinue Treatment/Off-Study Criteria". Therefore, any patient meeting this criteria will be deemed to have experienced an "unacceptable" toxicity for the purposes of the trial. For each study condition, we plan to enroll 12 patients in cohorts of size 6. All patients will be monitored for at least 4 months from the beginning of RT, before declaring the treatment acceptable for enrolling the next cohort of 6 patients.

Continuous monitoring using the method of Thall [20] will be employed for each study cohort of 12 patients in cohorts of size 6 where each patient is monitored for at least 4 months from the start of RT. We will stop the trail if we have reason to believe that the treatment-related toxicity rate is more than 30%. Using the following probability rule

Pr(rate of treatment-related toxicity 4 months from the start of RT > 30% | data) > 0.80.

If we determine there is more than a 80% chance that the treatment-related toxicity rate is more than 30%, we will stop the trial. We will assume a beta(0.6, 1.4) distribution for treatment-related toxicity as this prior provides a mean of 30% and a standard deviation of 26.5%. Thus the trial will be stopped if

[# of patients with treatment-related toxicity 4 months from day 1 of the start of RT / # of patients evaluated]

$$\geq 3/6, 6/12$$

Therefore, we will stop either study cohort if we observe 3 or more treatment-related toxicities in the first 6 patients, or if we observe 6 treatment related toxicities at any time while evaluating all 12 patients. We will suspend accrual while evaluating the first 6 patients to ensure none of

the stopping boundaries have been reached prior to enrolling the final 6 patients of each study cohort. The operating characteristics from this decision rule are shown in Table X and are based on 1000 simulations for each scenario.

Table X. Operating characteristics for toxicity monitoring rule

Treatment-related Toxicity 4 months after start of RX	Probability of Stopping Early	Sample Size Avg
0.10	0.017	11.9
0.20	0.099	11.4
0.30	0.254	10.5
0.40	0.462	9.2
0.50	0.650	8.1

- Operating Characteristics acquired using the Stata command stopbound

If the true toxicity rate is 0.50, there is a 65.0% probability of stopping the trial early.

Descriptive statistics will be used to summarize the study data. For each study cohort, we will tabulate toxicities by dose, severity, and relationship to the treatment plan. The method of Kaplan and Meier will be used to estimate median PFS and OS.

A Toxicity/Efficacy Summary will be submitted to the IND Medical Monitor after the first 6 evaluable subjects per cohort, complete 4 months from the initiation of Radiation Therapy and prior to the enrollment of the next cohort, and following the treatment of the next 6 evaluable subjects to each cohort.

8.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

8.1 Investigational Product

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

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

Table 7 Product Descriptions

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

8.2 Packaging and Labeling Information

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

8.3 Clinical Supplies Disclosure

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

8.4 Storage and Handling Requirements

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

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

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

8.5 Returns and Reconciliation

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

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

9.0 APPENDICES

9.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

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

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

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

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

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan,

D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

9.4 Events of Clinical Interest Guidance Document

Document attached as Appendix G in PDOL system.

10.0 REFERENCES

[1] Centers for Disease C, Prevention. Malignant mesothelioma mortality--United States, 1999-2005. MMWR Morbidity and mortality weekly report. 2009;58:393-6.
[2] Ahamad A, Stevens CW, Smythe WR, Liao Z, Vaporciyan AA, Rice D, et al. Promising early local control of malignant pleural mesothelioma following postoperative intensity modulated radiotherapy (IMRT) to the chest. Cancer journal. 2003;9:476-84.
[3] Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol. 2003;21:2636-44.
[4] Krug LM, Pass HI, Rusch VW, Kindler HL, Sugarbaker DJ, Rosenzweig KE, et al. Multicenter phase II trial of neoadjuvant pemetrexed plus cisplatin followed by extrapleural pneumonectomy and radiation for malignant pleural mesothelioma. J Clin Oncol. 2009;27:3007-13.
[5] Treasure T, Lang-Lazdunski L, Waller D, Bliss JM, Tan C, Entwisle J, et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. Lancet Oncol. 2011;12:763-72.
[6] Treasure T, Sedrakyan A. Pleural mesothelioma: little evidence, still time to do trials. Lancet. 2004;364:1183-5.
[7] Lang-Lazdunski L, Bille A, Lal R, Cane P, McLean E, Landau D, et al. Pleurectomy/decortication is superior to extrapleural pneumonectomy in the multimodality management of patients with malignant pleural mesothelioma. J Thorac Oncol. 2012;7:737-43.
[8] Chance WW, Rice DC, Allen P, Tsao A, Fontanilla H, Zhongxing L, et al. Postoperative hemithoracic intensity-modulated radiation therapy (IMRT) with an optional integrated boost for malignant pleural mesothelioma: toxicity, patterns of failure, and a matched survival analysis. ASTRO abstract. 2014.
[9] Rosenzweig KE, Zauderer MG, Laser B, Krug LM, Yorke E, Sima CS, et al. Pleural intensity-modulated radiotherapy for malignant pleural mesothelioma. International journal of radiation oncology, biology, physics. 2012;83:1278-83.
[10] Rimner A, Spratt DE, Zauderer MG, Rosenzweig KE, Wu AJ, Foster A, et al. Failure Patterns After Hemithoracic Pleural Intensity Modulated Radiation Therapy for Malignant Pleural Mesothelioma. International journal of radiation oncology, biology, physics. 2014.
[11] Liao ZX, Komaki RR, Thames HD, Jr., Liu HH, Tucker SL, Mohan R, et al. Influence of technologic advances on outcomes in patients with unresectable, locally advanced non-small-cell lung cancer receiving concomitant chemoradiotherapy. International journal of radiation oncology, biology, physics. 2010;76:775-81.

[12] Li H, Zhang X, Park P, Liu W, Chang J, Liao Z, et al. Robust optimization in intensity-modulated proton therapy to account for anatomy changes in lung cancer patients. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2015;114:367-72.
[13] Kesarwala AH, Ko CJ, Ning H, Xanthopoulos E, Haglund KE, O'Meara WP, et al. Intensity-modulated proton therapy for elective nodal irradiation and involved-field radiation in the definitive treatment of locally advanced non-small-cell lung cancer: a dosimetric study. Clin Lung Cancer. 2015;16:237-44.
[14] Kardar L, Li Y, Li X, Li H, Cao W, Chang JY, et al. Evaluation and mitigation of the interplay effects of intensity modulated proton therapy for lung cancer in a clinical setting. Practical radiation oncology. 2014;4:e259-68.
[15] Pan HY, Jiang S, Sutton J, Liao Z, Chance WW, Frank SJ, et al. Early experience with intensity modulated proton therapy for lung-intact mesothelioma: A case series. Practical radiation oncology. 2015.
[16] Cedres S, Ponce-Aix S, Zugazagoitia J, Sansano I, Enguita A, Navarro-Mendivil A, et al. Analysis of expression of programmed cell death 1 ligand 1 (PD-L1) in malignant pleural mesothelioma (MPM). PloS one. 2015;10:e0121071.
[17] Alley EM, R.; Santoro, A.; Beckey, K.; Yuan, S.S.; Cheng, J.; Piperdi, B.; Schellens, J.H.M. Clinical safety and efficacy of Pembrolizumab (MK-3475) in patients iwth malignant pleural mesothelioma (MPM): preliminary results from KEYNOTE-028. Proceedings of the American Association of Cancer Research, Philadelphia, PA, 2015. 2015.
[18] Chance WWR, D.C.; Allen, P.K.; Tsao, A.S.; Fontanilla, H.P.; Liao, Z.; Chang, J.Y.; Tang, C.; Welsh, J.S.; Mehran, R.J.; Gomez, D.R. Hemithoracic intensity modulated radiation therapy after pleurectomy/decortication for malignant pleural mesothelioma: toxicity, patterns of failure, and a matched survival analysis. International journal of radiation oncology, biology, physics. 2014;In press.
[19] Tucker SL, Jin H, Wei X, Wang S, Martel MK, Komaki R, et al. Impact of Toxicity Grade and Scoring System on the Relationship Between Mean Lung Dose and Risk of Radiation Pneumonitis in a Large Cohort of Patients With Non-Small Cell Lung Cancer. International journal of radiation oncology, biology, physics. 2009.
[20] Thall PF, Simon RM, Estey EH. Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. Stat Med. 1995;14:357-79.