PHASE II TRIAL OF CONSOLIDATION PEMBROLIZUMAB AFTER CONCURRENT CHEMOTHERAPY AND PROTON REIRRADIATION FOR THORACIC RECURRENCES OF NON-SMALL CELL LUNG CANCER

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Table of Contents

List of Abbreviations

CTCAE- Common Terminology Criteria for Adverse Events
CTEP - Cancer Therapy Evaluation Program
CTV – clinical target volume
ECOG - Eastern Cooperative Oncology Group
NCI – National Cancer Institute
NSCLC- non-small cell lung cancer
OS- overall survival
PD-1- programmed cell death 1
PFS- progression-free survival
ULN – upper limit of normal

Study Summary

Title	Phase II trial of consolidation Pembrolizumab after concurrent chemotherapy and proton reirradiation for thoracic recurrences of non-small cell lung cancer
Short Title	Phase II of Pembrolizumab after chemotherapy and proton reirradiation for recurrent NSCLC
Protocol Number	UPCC 16516//IRB 825877
Phase	Phase II
Methodology	Single arm, open label
Study Duration	2 - 2.5 years
Study Center(s)	Single-center (The Hospital of the University of Pennsylvania and Penn Presbyterian Medical Center)
Objectives	The primary objective is progression-free survival. Secondary objectives include overall survival and toxicity determination.
Number of Subjects	41
Diagnosis and Main Inclusion Criteria	Patients with a histologic or cytologic diagnosis of NSCLC who have received previous intrathoracic radiation therapy with definitive intent and have a tumor recurrence in or near the prior irradiation fields, age 18 or older, with an ECOG performance status of 0 to 1.
Study Product, Dose, Route, Regimen	Pembrolizumab 200 mg intravenously approximately every 21 days for 17 cycles (about 12 months).
Duration of administration	Pembrolizumab will be started 4 to 12 weeks after completion of proton reirradiation +/- concurrent chemotherapy. Pembrolizumab will be given at a dose of 200 mg intravenously every 21 days for 17 cycles (about 12 months) if there is no evidence of progressive disease or intolerable side effects.
Reference therapy	The study product is being compared to historical controls
Statistical Methodology	A single arm phase II study will enroll 41 patients over 2 years. Patients will be followed for an additional 3 months after enrollment has ended. At the final analysis there will be 80% power to detect an improvement in median progression-free survival from 6 months (historical rate) to 10 months, assuming exponential survival and 1-sided 5% significance level. Median progression-free survival and overall survival will be estimated by the Kaplan-Meier method.

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Isolated local or regional recurrences of non-small cell lung cancer (NSCLC) in or near previously irradiated thoracic fields present a therapeutic challenge. Rather than using systemic therapy alone, instituting localized therapy is appealing given our generally poor response rates to salvage chemotherapy, particularly in tumors that arise in previously irradiated fields. However, surgery and radiation therapy are both technically difficult and pose high toxicity risks in this setting. Conventionally fractionated thoracic reirradiation for recurrent lung cancer has yielded 1-year local progression-free survival (PFS) rates as high as 51% [1-6], but its widespread use has been limited by toxicities. Given these positive results, proton reirradiation has been utilized as a potential strategy to minimize harm to surrounding tissues while treating a local recurrence aggressively. A multicenter study presented at the 2013 ASCO Annual Meeting reported encouraging early outcomes, with a median PFS of 14 months, and acceptable toxicity for proton reirradiation in an initial cohort of patients treated with low-volume clinical target volumes [7]. Since proton reirradiation is a promising new tactic to treat thoracic recurrences of NSCLC that can potentially minimize toxicities compared with photon reirradiation, additional strategies to improve outcomes with this modality are warranted.

Pembrolizumab is an anti-PD-1 immunotherapy that has demonstrated activity in several different types of cancers, including lung cancer. Because of its potentially enhanced efficacy when used in minimal disease states, Pembrolizumab may be well suited as “consolidation” therapy for localized recurrences treated with chemoradiation [8]. The combination of radiation therapy and immunotherapy may improve treatment responses through several different mechanisms [8]. Preclinical studies in mice show that anti-PD1 therapy enhances the efficacy of radiation therapy via a T cell dependent cytotoxic mechanism [9]. Immune cell recognition of tumor cells may be increased after radiation therapy [10] due to the release of additional tumor specific antigens leading to a heightened T-cell immune response driven by antigen-presenting cells [8]. Radiation therapy can also decrease immune tolerance due to a large tumor burden [8, 11], potentially increasing the success of immune therapies. Recent parallel preclinical and clinical studies suggest that PD-L1 upregulation by cancer cells may emerge as a resistance mechanism after treatment with anti-CTLA4 therapy plus radiation. Adding anti- PD-L1/PD-1 therapy may be of benefit in this situation [12].

The cytotoxic effects of chemotherapy may potentially enhance the effects of immunotherapy in a similar fashion to radiation therapy. There is evidence supporting a potential advantage to sequential chemotherapy followed by immune therapy. In the clinical setting, NSCLC patients receiving Ipilimumab, an anti-CTLA4 monoclonal antibody, experienced improved immune related PFS when it was phased into treatment after 2 cycles of chemotherapy, compared to chemotherapy alone, potentially from the mechanisms proposed [13]. Conversely, those individuals who started Ipilimumab concurrently with chemotherapy during cycle #1 did not have a statistically significant PFS or overall survival (OS) advantage.

Based on previous data strongly suggesting that Pembrolizumab may have its optimal benefit in states of minimal disease, and pre-clinical and clinical evidence that immunotherapies that target the CTLA4 and PD-1 pathways can be used effectively with radiation therapy and chemotherapy and potentially work synergistically with these treatment modalities, we propose a phase II trial of consolidation

Pembrolizumab after concurrent chemotherapy and proton reirradiation for thoracic recurrences of NSCLC. PFS will be our main endpoint.

1.2 Investigational Agent

The programmed cell death 1 (PD-1) pathway represents a major immune control switch, which may be engaged by tumor cells to overcome active T-cell immune surveillance. Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection.

1.3 Preclinical Data

The importance of intact functions of immune surveillance in controlling outgrowth of neoplastic transformations has been known for decades [14]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes 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 (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and re-infused, inducing durable objective tumor responses in cancers such as melanoma [15, 16].

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 immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [17, 18]. The structure of murine PD-1 has been resolved [19]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail 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, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch 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 [18, 20-22]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [23, 24]. 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 [25, 26]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells, as well as subsets of macrophages and dendritic cells [27]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types including nonhematopoietic tissues and in various tumors [14, 24, 28-30]. Both ligands are type 1 transmembrane receptors containing IgV-like and Ig constant–like (IgC-like) domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-L1 or PD-L2 to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various nonhematopoietic tissues, most notably on vascular endothelium; whereas PD-L2 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 [24]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including renal cell carcinoma [31], pancreatic carcinoma [32], hepatocellular carcinoma [33], and

ovarian carcinoma [34]. Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma [35].

The observed correlation of clinical prognosis with PD-L1 expression in multiple cancers 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.

Therapeutic studies in mouse models show that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatment modalities. Anti–mouse PD-1 and anti–mouse PD-L1 have demonstrated antitumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-γ, granzyme B, and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [32, 36-40]. In addition, the combination of gemcitabine and anti–PD-L1 mAb demonstrated synergy in the rejection of pancreatic mouse tumors [32]. In-house experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models.

Pembrolizumab strongly enhances T-lymphocyte immune responses in cultured blood cells from healthy human donors, cancer subjects, and nonhuman primates. In T-cell activation assays using human donor blood cells, the half-maximal effective concentration (EC50) has been approximately 0.1 to 0.3 nM. In addition to interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFN□), and levels of other cytokines were found to be modulated by pembrolizumab. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T-cells. In the in vitro peripheral blood mononuclear cell (PBMC) and whole blood cytokine release assays, the cytokine levels induced by pembrolizumab were low and comparable to those induced by trastuzumab. Pembrolizumab does not induce antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC).

Using anti–murine PD-1 surrogate antibodies, PD-1 blockade has been shown to significantly inhibit tumor growth in a variety of syngeneic murine tumor models. In these experiments in mice, anti–PD-1 therapy is synergistic with chemotherapeutic agents such as gemcitabine and 5-fluorouracil (5-FU), and combination therapy results in increased complete tumor regression rates in vivo. Studies also revealed that immunosuppressive doses of dexamethasone included in combination with agents used in standard-of-care treatment for NSCLC do not reduce the anti-tumor efficacy of an anti–murine PD-1 surrogate antibody.

1.4 Clinical Data to Date

Immuno-modulatory agents recently showed promising efficacy in multiple cancer types. Two Phase III studies of IPI, an anti-CTL4 mAb, showed significant prolongation of OS in subjects with melanoma [41, 42]. Recent data with anti–PD-1 antibodies have validated PD-1 as an attractive target for clinical intervention [43-45]. Importantly, responses have been of long duration and pembrolizumab is generally well tolerated. Based on these data and considerations, the anti–PD-1 antibody, pembrolizumab, appears to be an attractive candidate for continued clinical development in cancer.

As of the data cutoff dates for Merck's most recent Investigator's Brochure, the safety and efficacy of pembrolizumab treatment in subjects with hematologic malignancies and solid tumors have been evaluated in 18 ongoing, Merck-sponsored clinical trials (please refer to the Investigator's Brochure for details).

1.5 Dose Rationale and Risk/Benefits

An open-label Phase I trial (Protocol 001) evaluating Pembrolizumab at 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks revealed no dose-limiting toxicities and showed objective evidence of tumor size reduction at all dose levels. Recent data from other clinical studies in the Pembrolizumab

program have 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. Within the resulting population PK model, clearance and volume parameters of Pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. 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 every 3 weeks 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 every 3 weeks vs. the dose regimen of 2 mg/kg every 3 weeks (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings, and this trial will use the 200 mg every 3 weeks fixed dose regimen.

2 Study Objectives

Primary Objective

1.) To assess PFS in subjects treated with consolidation Pembrolizumab after concurrent chemotherapy and proton reirradiation for thoracic recurrences of NSCLC.

Secondary Objective

1.) To assess OS in subjects treated with consolidation Pembrolizumab after concurrent chemotherapy and proton reirradiation for thoracic recurrences of NSCLC.

2.) To determine toxicities (Common Terminology Criteria for Adverse Events (CTCAE) v5.0 scoring) of consolidation Pembrolizumab after concurrent chemotherapy and proton reirradiation

4.) To evaluate PFS and OS as a function of PD-L1 expression, as well as other emerging indices of benefit.

3 Study Design

3.1 General Design

This is a phase II, single arm, unblinded trial of about 12 months of consolidation Pembrolizumab after proton reirradiation with or without concurrent chemotherapy for isolated local and regional thoracic recurrences of NSCLC. Forty-one patients will be treated with re-irradiation with or without standard concurrent chemotherapy to all gross disease with proton beam therapy. The intended radiation dose should be at least 60 Gy of reirradiation in 1.8-2.0 Gy fractions with or without concurrent chemotherapy or in 4.0 Gy fractions without chemotherapy, at the provider's discretion. This corresponds to daily fractionated radiation over a period of approximately 3-8 weeks. Four to 12 weeks after completing reirradiation, patients will begin Pembrolizumab consolidation. Pembrolizumab will be given at a fixed dose of 200 mg intravenously approximately every 21 days for 17 cycles (about 12 months) if there is no evidence of progressive disease or intolerable side effects.

Subjects will be evaluated approximately 30 days prior to consolidation Pembrolizumab and every 12 weeks (1 day after until the day of the next infusion) while on Pembrolizumab with radiographic imaging to assess disease status. If new signs or symptoms of progression occur between scheduled scans, directed imaging will be obtained at the clinically appropriate time point to document disease status. Investigators will make all treatment-based decisions using RECIST 1.1. Adverse events will be monitored upon initiation of Pembrolizumab treatment and continue throughout the trial and graded in severity according to the National Cancer Institute (NCI) CTCAE version 5.0. For the

Pembrolizumab phase, all treatment-related toxicities will be recorded.

Treatment with Pembrolizumab will continue for 17 cycles (about 12 months) in the absence of (1), documented disease progression, (2) unacceptable adverse event(s), (3) intercurrent illness that prevents further administration of treatment, (4) investigator's decision to withdraw the subject, (5) subject withdrawal of consent, (6) pregnancy of the subject, (7) noncompliance with trial treatment or procedure requirements, (8) institution of alternative systemic treatment, or (9) other administrative reasons. After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring (serious adverse events will be collected for up to 90 days after the end of treatment). Subjects will have post-treatment follow-up for disease status until one of the following events: (1) disease progression; (2) initiation of non-study cancer treatment; (3) withdrawal of study consent; (4) loss to follow-up or (5) death. In addition, survival status beyond the establishment of PD or initiation of subsequent therapies will be documented.

The primary objective of the trial includes determination of PFS per RECIST 1.1. Secondary objectives include OS and safety/toxicity determination as assessed by a variety of parameters of adverse events (AEs), including incidence and time to first Grade 3-5 AE. Pre-specified adverse events of clinical interest during the Pembrolizumab phase include the following events: 1) Grade ≥ 3 diarrhea 2) Grade ≥ 2 colitis, 3) Grade ≥ 2 pneumonitis, 4) Grade ≥ 3 hypo- or hyperthyroidism, 5) Grade ≥ 2 hypophysitis, 6) Grade ≥ 2 uveitis, and 7) Grade ≥ 2 nephritis. Participation in this trial will encourage supplying tumor tissue from either a newly obtained formalin-fixed specimen (preferred) or an older formalin-fixed, paraffin-embedded specimen, from locations not radiated prior to biopsy. The specimen will be evaluated at a central laboratory facility for expression status of PD-L1 in a retrospective manner. Eligibility for the trial will not be dependent upon PD-L1 expression status, but the sponsor may amend the trial in the future if new data arise regarding the predictive value of PD-L1 expression. Any patient enrolled on the study prior to such an amendment, however, will remain on study.

3.2 Primary Study Endpoints

The primary endpoint is PFS, which measures the length of time from the first day of proton reirradiation +/- concurrent chemoradiation until progressive disease, death from any cause, or last patient contact.

3.3 Secondary Study Endpoints

Secondary endpoints include the following:

1. OS: measures the length of time from the first day of proton reirradiation +/- concurrent chemoradiation to death from any cause or last patient contact.

2. Toxicity: CTCAE v5.0 scoring

Exploratory analysis of PDL-1 expression and other biomarkers in this setting will also be performed.

3.4 Primary Safety Endpoints

The safety and tolerability of consolidation Pembrolizumab after concurrent chemotherapy and proton reirradiation will be evaluated. Clinical assessment and laboratory evaluation of Adverse Events and Dose Limiting Toxicities will be done according to the CTCAE, version 5.0 of the NCI Cancer Therapy Evaluation Program (CTEP).

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

1. Histologic or cytologic diagnosis of NSCLC who have received previous intrathoracic radiation therapy with definitive intent and have a tumor recurrence in or near the prior irradiation fields.

Re-biopsy of the recurrence is not required and is left to the discretion of the treating physician, although every effort should be made to confirm recurrence pathologically.

2. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1
3. Age 18 or greater
4. Patients with prior invasive malignancies are allowed, provided they have been treated with definitive intent and have no evidence of active disease requiring treatment in the past 2 years.
5. Patients must be capable of giving informed consent and be willing and able to comply with schedule.
6. Serum total bilirubin $\leq$ 1.5 X upper limit of normal (ULN) OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN prior to Pembrolizumab treatment.
7. Platelets >100,000 cells/mm3 and ANC $\geq$ 1,250 cells/mm^3 prior to Pembrolizumab treatment.
8. Creatinine ≤ 1.5 X ULN OR measured or calculated creatinine clearance ≥50 mL/min for subject with creatinine levels > 1.5 X institutional ULN. (GFR can also be used in place of creatinine or CrCl) prior to Pembrolizumab treatment
9. Clinical target volume (CTV) size must be <250 cc, no more than 74 Gy of prior radiation in 2 Gy fractions previously administered.

4.2 Exclusion Criteria

1. Allergy to Pembrolizumab or related compounds
2. History of symptomatic CTCAEv5 grade ≥3 pneumonitis following the initial course of definitive radiation therapy
3. History of symptomatic idiopathic pulmonary fibrosis or interstitial lung disease
4. Use of continuous oxygen
5. Diagnosis of immunodeficiency or exposure to systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. (Nasal or oral inhalers are permissible).
6. Active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy are an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections are not excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome are not excluded from the study.
7. History of allogenic tissue or solid organ transplant
8. Prior immunotherapy less than 30 days from the planned start of reirradiation
9. Patients with known extrathoracic metastases, including brain metastases, or known malignant pleural or pericardial effusion
10. Prior radiation treatment less than 6 months from the planned start of reirradiation of any part of the intended treatment volume
11. Pregnant or breast-feeding patients. Men and women of reproductive potential may not participate in this study unless they have agreed to use an effective contraceptive method while in this study.
12. Known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
13. Known active Hepatitis B (e.g., HBsAg positive or HBV DNA detectable) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

4.3 Subject Recruitment and Screening

Subjects will be recruited for this study from the clinical practices of the Abramson Cancer Center at the University of Pennsylvania and Penn Presbyterian Medical Center. Subjects will be required to give written informed consent to participate in the study before any screening tests or evaluations are conducted that are not part of standard care.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects who do not complete the study protocol will be considered to have prematurely discontinued the study. The reasons for premature discontinuation (for example, voluntary withdrawal, toxicity, death) must be recorded on the case report form (CRF). Final study evaluations will be completed at the time of discontinuation. Reasons for withdrawal include, but are not limited to, the following:

1. Inter-current illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree or require discontinuation of study drugs;
2. Unacceptable toxicity: Patients will be followed until resolution or stabilization;
3. Disease progression;
4. Withdrawal of patient consent;
5. Patient opting out of further treatment in the absence of progressive disease or significant comorbidity but still willing to have follow up regarding disease status;
6. Treatment delay greater than four weeks beyond the schedule for any toxicity
7. Non- compliance with study procedures that cannot be resolved;
8. Major protocol violations, including, but not limited to:
    1. failure to meet inclusion/exclusion criteria;
    2. failure to complete evaluations as required by protocol;
    3. use of concomitant therapies other than specified above.

The reason(s) for withdrawal should be noted in the case report form and in the patient's medical record. Standard supportive therapy should be maintained for subjects withdrawn from active treatment. Long-term follow-up data, including survival and progression data, will be collected.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Patients taken off study due to toxicity will be followed until resolution or stabilization. All patients will be followed for PFS and OS data.

5 Study Drug

5.1 Description

Pembrolizumab is a humanized anti–programmed cell death 1 (anti–PD-1) monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4)/kappa isotype with a stabilizing S228P sequence alteration in the fragment crystallizable (Fc) region. Pembrolizumab binds to human PD-1 and blocks the interaction between PD-1 and its ligands. The theoretical molecular weight of the polypeptide is 146,288 daltons (Da) and its theoretical isoelectric point (pI) is 7.5. The parental murine anti–human PD-1 antibody (hPD-1.09Å) was produced by immunizing mice with hPD-1 DNA. The pembrolizumab antibody was generated by humanization of the parental antibody by the Medical Research Council (Cambridge, UK) using complementarity determining region grafting technology (U.S. Patent No. 5,225,539). The gene segments encoding the variable heavy and light chains of pembrolizumab, as well as human IgG4, were codon-optimized, synthesized, and ligated into a vector.

A single expression plasmid, pAPD11V1-GA, was constructed for the expression of both the heavy and light antibody chains of pembrolizumab. The nucleotide sequences encoding the heavy and light chains, along with their respective promoters and poly A signal sequences, have been confirmed by

DNA sequence analysis. The pAPD11V1-GA expression vector was subsequently used to transfect CHO-DXB-11 cells for the development of the pembrolizumab-producing cell line.

5.2 Treatment Regimen

Patients will be treated with reirradiation with or without standard concurrent chemotherapy to all gross disease with proton beam therapy. The intended radiation dose should be at least 60 Gy of reirradiation in 1.8-2.0 Gy fractions with or without concurrent chemotherapy or in 4.0 Gy fractions without chemotherapy, at the provider's discretion. This corresponds to daily fractionated radiation over a period of approximately 3-8 weeks. The decision to use concurrent chemotherapy, and which regimen to utilize, are left to the discretion of the treating oncologist. The chemotherapy regimen and doses will be recorded in the patient record.

Pembrolizumab will be started 4 to 12 weeks after completion of reirradiation. Pembrolizumab will be given at a dose of 200 mg intravenously approximately every 21 days for 17 cycles (about 12 months) if there is no evidence of progressive disease or intolerable side effects.

Dose Modifications (Escalation/Titration/Other)

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 3 below. See Section 5.6 for supportive care guidelines, including use of corticosteroids.

Table 1: Dose Modification Guidelines for Drug-Related Adverse Events

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

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

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

[a] 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.

[b] 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; Refer to Infusion Treatment Guidelines for further management details.

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

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

5.3 Preparation and Administration of Study Drugs

A research supply of Pembrolizumab will be supplied by Merck. It will be shipped to, stored and dispensed from Investigational Drug Services (IDS) of the Hospital of the University of Pennsylvania and Penn Presbyterian Medical Center for patients enrolled at that site. The drug preparation will be done in the pharmacy.

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 2.

Table 2: Product Descriptions

Product Name and Potency	Dosage Form
Pembrolizumab 100 mg/4mL	Solution for injection

Study Medication Administration

Pembrolizumab will be administered as a 30 minute intravenous infusion (treatment cycle intervals may be increased due to toxicity as described in Table 1). 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).

Pembrolizumab Premedication

Patients do not require premedication prior to Pembrolizumab administration, as hypersensitivity reactions are rare.

5.4 Subject Compliance Monitoring

The study team will track subject compliance with the treatment regimen at each visit and note the dose, date, and time of study medication administration on the case report form. If there are any significant irregularities in compliance (in the opinion of the investigator), the subject should be withdrawn from the study. Interruptions from the protocol specified treatment plan for greater than 12 weeks between Pembrolizumab doses due to toxicity will require consultation between the investigator and the medical monitor and written documentation of the collaborative decision on subject management.

5.5 Prior and Concomitant Therapy

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 Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the Investigator, the Sponsor, and the subject.

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medications will be recorded in the subject's medical record 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 in the medical record. Examples of acceptable concomitant medications include zoledronic acid, denosumab, megestrol acetate, and cannabinoids.

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.

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Pre-Pembrolizumab Screening and Pembrolizumab Treatment Phase of this trial:

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy 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 after consultation with Sponsor, but would be regarded as a disease progression event for the primary outcome.
- 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, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal

influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines and are not allowed.

- Glucocorticoids for any purpose other than an abbreviated course to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic replacement doses of corticosteroids may be approved after consultation with the Sponsor.

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

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

5.6 Rescue Medications and Supportive Care

5.6.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these 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 does not need to follow the treatment guidance (as outlined below). Refer to Section 5.2.1 for dose modification.
It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

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

  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
    - For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.
    - For **Grade 3 or 4 diarrhea/colitis,** 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.

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

Table 1 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.6.1.1 Supportive Care Guidelines for Events of Clinical Interest and Immune-related Adverse Events (irAEs)

Events of clinical interest of a potential immunologic etiology (irECIs) may be defined as an adverse event of unknown etiology, associated with drug exposure and consistent with an immune

phenomenon. irAEs may be predicted based on the nature of Pembrolizumab, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE. Information on how to identify and evaluate irAEs has been developed. Subjects who develop a Grade 2 or higher irAE should be discussed immediately with the Sponsor.

Recommendations to managing irAEs not detailed elsewhere in the protocol are detailed in Table 4 and the irAE guidance document (attached Appendix).

Table 4: General Approach to Handling irAEs

irAE	Withhold/Discontinue Pembrolizumab?	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold Pembrolizumab	Consider systemic corticosteroids in addition to appropriate symptomatic treatment
Grade 3 and Grade 4	Withhold Pembrolizumab Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 12 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.

5.6.1.2 Supportive Care Guidelines for Pneumonitis

Subjects with symptomatic pneumonitis should immediately stop receiving Pembrolizumab and have an evaluation. The evaluation may include bronchoscopy and pulmonary function tests to rule out other causes such as infection. If the subject is determined to have study drug associated pneumonitis, the suggested treatment plan is detailed in Table 5.

Table 5: Recommended Approach to Managing Pneumonitis

Study drug associated pneumonitis	Withhold/Discontinue Pembrolizumab?	Supportive Care
Grade 1 (asymptomatic)	No action	Intervention not indicated
Grade 2	Withhold Pembrolizumab, may resume treatment if improves to Grade 1 or resolves within 12 weeks	Systemic corticosteroids are indicated. Taper if necessary.

Grade 3 and Grade 4	Permanently discontinue Pembrolizumab	Systemic corticosteroids are indicated. The use of infliximab may be indicated as appropriate.

For Grade 2 pneumonitis that improves to ≤ Grade 1 within 12 weeks, the following rules should apply:

- First episode of pneumonitis
    - May increase dosing interval by one week in subsequent cycles
- Second episode of pneumonitis – permanently discontinue Pembrolizumab if upon rechallenge subject develops pneumonitis ≥ Grade 2

5.7 Contraception and Pregnancy

5.7.1 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 for the duration of the study and during the follow-up period. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.2 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 without delay and within 24 hours 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 followed as described above and in Section 8.2.2.

5.7.3 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

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

- Withdrawal of consent.
- Confirmed radiographic disease progression

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, as consistent with irRC.
- Unacceptable adverse experiences or toxicities
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- Confirmed positive serum pregnancy test and unwillingness to abort pregnancy
- Noncompliance with trial treatment or procedure requirements
- Loss to follow-up
- Completion of 17 cycles (about 12 months) of treatment with Pembrolizumab
- Other Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 7 (Protocol Flow Chart). 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). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiation of non-study cancer treatment, withdrawal of consent or loss to follow-up. After documented disease progression each, subject will be followed by telephone or chart review for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first. All subsequent therapies will be recorded, if feasible.

5.9 Subject Replacement Strategy

Subjects who receive at least 1 dose of proton reirradiation will be considered evaluable and will not be replaced.

5.10 Clinical Criteria for Early Trial Termination

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

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

2. Poor adherence to protocol and regulatory requirements

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

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

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

6 Labeling, Packaging, Storage and Return of Clinical Supplies

6.1 Labeling

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

6.2 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. They will be stored in the Investigational Drug Pharmacy as part of the Abramson Cancer Center.

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.

6.3 Returns and Reconciliation

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

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

7 TRIAL FLOW CHART

7.1 Trial Flow Chart

Table 6: Study procedures by visit

Trial Period:	**Screening Phase**	**Proton Reirrad-iation +/- Chemo-therapy**	**Pembrolizumab Treatment Cycles***									**Post-Treatment**	
Treatment Cycle /Title:	Screening	Reirradi-ation	1/9	2/10	3/11	4/12	5/13	6/14	7/15	8/16	17	Safety Follow-up	Follow Up Visits
Scheduling Window (Days):	-28 to -1	Daily protons for 3-8 weeks	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At last treat-ment	30 days post tx/discon	Every 3 months for 2 yrs
Administrative Procedures													
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Demographics and Medical History	X												
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X		
Trial Treatment Administration			X	X	X	X	X	X	X	X	X		
Post-study anticancer therapy status												X	X
Survival Status		X	X	X	X	X	X	X	X	X	X	X	X
Clinical Procedures/Assessments													
Review Adverse Events**			X	X	X	X	X	X	X	X	X	X	X
Full Physical Examination	X					X				X		X	X
Directed Physical Examination		X	X	X	X		X	X	X		X		
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	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												
PT/INR and aPTT	X												
CBC with Differential	X			X	X	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry	X			X	X	X	X	X	X	X	X	X	X

Trial Period:	Screening Phase	Proton Reirrad-iation +/- Chemo-therapy	Pembrolizumab Treatment Cycles*									Post-Treatment	
Treatment Cycle /Title:	Screening	Reirradi-ation	1/9	2/10	3/11	4/12	5/13	6/14	7/15	8/16	17	Safety Follow-up	Follow Up Visits
Scheduling Window (Days):	-28 to -1	Daily protons for 3-8 weeks	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At last treat-ment	30 days post tx/discon	Every 3 months for 2 yrs
Urinalysis	X					X				X		X	
T3, FT4 and TSH	X			X			X			X		X	
Efficacy Measurements													
Tumor Imaging	X***	X	X				X, X				X		X
Tumor Biopsies/Archival Tissue Collection/Correlative Blood Studies													
Archival or Newly Obtained Tissue Collection (optional)	X												
Correlative Studies Blood Collection	X			X				X		X	X	X	

For the Pembrolizumab phase, we will report all treatment-related toxicities.
***The Pre-Screening visit and Main Study Screening visit may be combined to one Study Screening visit in some patient circumstances**
***Cycles 9-17 are to be repeated using same trial flow chart as cycles 1-8**
****AEs will be monitored for one year following treatment for patients who complete all 17 cycles of Pembrolizumab. AEs will be followed for 30 days, and SAEs for 90 days, for patients who discontinue the study early for any reason.**
*****Baseline tumor imaging may occur up to 42 days before starting standard of care treatment**

8 TRIAL PROCEDURES

8.1 Trial Procedures

The Trial Flow Chart (**Table 6**) 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. If a procedure is performed according to institutional standard of care, it will fall under SOC guidelines and not this protocol.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor for reasons related to subject safety. In these cases, such evaluations/testing will be performed in accordance with those regulations.

8.1.1 Administrative Procedures

8.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial. Documentation of the informed consent process must be placed in the electronic medical record. We will also utilize Telemedicine for consenting patients and obtain electronic signatures.

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.

For Telemedicine consent, the staff will have access to a computer with a camera and a dedicated and private room for all telemedicine encounters. It will be pre-determined that the potential subject has access to a computer, iPad, or phone with a camera and a My Penn Medicine account. Consent forms will be sent prior to the telemedicine encounter. Subjects can e-sign the document, at which point the consent form becomes part of their EMR, and they can print it from My Penn Medicine.

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.

8.1.1.2 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. Waivers will not be granted without the explicit approval of the study medical monitor and IRB/CTSRMC.

8.1.1.3 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.

8.1.1.4 Prior and Concomitant Medications Review

8.1.1.4.1 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.

8.1.1.4.2 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 8.2.

8.1.1.5 Disease Details and Treatments

8.1.1.5.1 Disease Details

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

8.1.1.5.2 Prior Treatment Details

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

8.1.1.5.3 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.

8.1.1.6 Trial Compliance (Medication/Diet/Activity/Other)

Interruptions from the protocol specified treatment plan for greater than 12 weeks between Pembrolizumab doses due to toxicity will require consultation between the investigator and the medical monitor and written documentation of the collaborative decision on subject management.

8.1.2 Clinical Procedures/Assessments

8.1.2.1 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 after the start of Pembrolizumab and during the follow-up period according to NCI CTCAE Version 5.0. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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 (irAE). See Section 5.7.1.1 and the irAE guidance document (attached Appendix) regarding the identification, evaluation and management of AEs of a potential immunological etiology.

Please refer to section 8.2 for detailed information regarding the assessment and recording of AEs.

8.1.2.2 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.

8.1.2.3 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.

8.1.2.4 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 7.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

8.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

8.1.2.6 Tumor Imaging and Assessment of Disease

The initial tumor imaging will be performed within 42 days prior to the first day of proton reirradiation or as indicated according to standard of care. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 30 days prior to the first day of treatment. Tumor imaging will be repeated at the conclusion of chemoradiation and within approximately 30 days prior to the first dose of pembrolizumab. Imaging while on pembrolizumab will be performed every 12 weeks (1 day before Pembrolizumab up until the day of the next infusion) after the first dose of pembrolizumab or more frequently if clinically indicated. Tumor imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of Pembrolizumab cycle frequencies. This image schedule will also be adjusted per subject's insurance coverage.

For patients that receive at least one dose of Pembrolizumab, after the first documentation of progression (if the subject is clinically stable) confirmatory scans may be performed as early as 28 days later; alternately, the scan performed at the next scheduled time point (e.g. every 84 ±7 days) may be used as confirmation.

After the first documentation of progression, it is at the discretion of the investigator either to verify true PD, to keep a clinically stable subject on trial treatment or to stop trial treatment until repeat imaging performed at least 28 days later confirms progression. Clinical Stability is defined as:

1) Absence of symptoms and signs indicating clinical significant progression of disease (including worsening of laboratory values) indicating disease progression.
2) No decline in ECOG performance status.
3) Absence of rapid progression of disease or progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

Subjects who are deemed clinically unstable are not required to have repeat imaging for confirmation. If progression is confirmed, then the subject will be discontinued from trial treatment. If progression is not confirmed, then the subjects should resume/continue trial treatment and have their next scan after two more cycles of treatment which would be approximately 6 weeks from the date of the scan that first showed progression. When feasible, subjects should not be discontinued until progression is confirmed.

For subjects who complete all treatment cycles, imaging during the follow-up period should be repeated approximately every 3 months for up to two years or until confirmation of progressive disease. Imaging during the follow-up period is to be repeated approximately every 3 months for subjects who discontinue trial treatment for reasons other than disease progression until the subject experiences confirmed disease progression or starts a new antineoplastic therapy.

The same imaging techniques should be used in a subject throughout the trial. For patients with

brain metastases, MRI brain should be included in the imaging follow up prior to treatment and at any time when a patient develops new neurologic symptoms. Ideally, CT scans should be used in lieu of PET imaging as the means of determining tumor status. But PET imaging may be used to confirm PD, if suspected, but not yet clear.

8.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial of Pembrolizumab to post-trial of Pembrolizumab visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject may vary depending upon clinical course of the subject and length of time on trial.

8.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 7. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial of Pembrolizumab to post-trial of Pembrolizumab visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject may vary depending upon clinical course of the subject and length of time on trial. Blood testing done during the reirradiation +_/-chemo phase will be done per standard of care.

Table 7: 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		Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide	results are noted	Free tyroxine (T4)
	(CO_2 or biocarbonate)	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Calcium		
	Chloride		Blood for correlative studies
	Glucose		
	Potassium		
	Sodium		
	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.			

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 Pembrolizumab.

8.1.3.1.1 Blood Collection for Additional Correlative Samples

Sample collection, storage and shipment instructions for blood samples may vary. Correlative samples will be used to examine Anti-Pembrolizumab Antibodies, inflammatory markers, circulating tumor cells and genetic analysis. These studies will be done upon receipt of additional funding; until that time samples will be stored as per local policy.

8.1.4 Other Procedures

8.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation when possible. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.2 - Assessing and Recording Adverse Events. After discontinuing treatment, these subjects should return to the site for a Safety Follow-up Visit (described in Section 8.1.5.4) and then proceed to the Follow-Up Period of the study (described in Section 8.1.5.5).

8.1.5 Visit Requirements

Visit requirements are outlined in Section 7.0 - Trial Flow Chart.

8.1.5.1 Screening

Visit requirements are outlined in Section 7.0 - Trial Flow Chart.

Prior to treatment initiation of Pembrolizumab, potential subjects will be evaluated to determine that they fulfill the entry requirements. Screening procedures may be repeated.

Written informed consent must be obtained prior to performing any protocol specific procedure.

Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 42 days prior to the first dose of trial treatment of Pembrolizumab except for the following:

- Laboratory tests are to be performed within 10 days prior to the first dose of trial treatment of Pembrolizumab.
- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of a repeating a screening test if performed within the specified time frame and the results meet the inclusion/exclusion criteria.

8.1.5.2 Proton Reirradiation +/- Chemotherapy

Subjects will be treated with proton re-irradiation with or without standard concurrent chemotherapy to all gross disease. The chemotherapy regimen and doses will be recorded.

Visit requirements are outlined in Section 7.0 - Trial Flow Chart.

8.1.5.3 Pre-Pembrolizumab Screening

Visit requirements are outlined in Section 7.0 - Trial Flow Chart.

Subjects will be eligible to move on to pembrolizumab treatment cycles if they received at least 50 Gy of reirradiation, if they have no progressive disease on tumor imaging, and if they do not have symptomatic CTCAEv5 grade ≥3 pneumonitis.

8.1.5.4 Pembrolizumab Treatment Cycles

Visit requirements are outlined in Section 7.0 - Trial Flow Chart.

8.1.5.5 Post-Treatment Visits

Visit requirements are outlined in Section 7.0 - Trial Flow Chart. Patients will be followed for up to 5 years for both PFS and OS status. After the completion of all therapy, subjects should be followed for up to 5 years, with no option for retreatment with Pembrolizumab on study.

8.1.5.6 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.

8.1.5.7 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 approximately every 3 months by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until disease progression, death, or end of the study. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

8.1.5.8 Survival Follow-up

Once a subject experiences confirmed disease progression, the subject moves into the survival follow-up phase and should have their medical record reviewed every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. A patient who has not experienced disease progression 3 years after enrollment may have his/her follow up visits and scans spaced out to every 6 months (24 weeks), at the discretion of the treating oncologist.

8.2 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.

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.

All adverse events will be recorded from beginning with cycle 1 of Pembrolizumab through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. Laboratory AE's will also start being recorded beginning with cycle 1 of Pembrolizumab. The reporting timeframe for adverse events meeting any serious criteria is described in section 8.2.3.1.

Applicable reporting to DSMC will occur as follows:

On-Site subjects (this includes any subjects enrolled at other sites on an in-house study)

1. All grade 3 or higher events (AE or SAE) within five business days of knowledge.
2. All unexpected deaths within 24 hours of knowledge.
3. All others deaths within 30 days of knowledge. Deaths of subjects off-study for greater than 30 days from the last study treatment/intervention are not reportable with the following exceptions:

Study Exceptions the CTSRMC will not Approve:

Exceptions to eligibility, treatment/dosing, contraindicated treatment/therapies/interventions or safety tests will not be approved for any of the following types of studies:

1. Any investigator-initiated treatment study.
2. Any investigator-initiated study utilizing an intervention with therapeutic intent.
3. Any Phase III study, regardless of sponsor (in-house, cooperative group, industry, consortium, etc.).
4. Any study involving on-campus manufacturing of any component, regardless of sponsor. 5. Any first in-human study.

Requests that fall into any of the above categories will receive an automatic rejection "The DSMC has rejected this request."

Exception

A one time, intentional action or process that departs from the IRB and CTSRMC approved study protocol, intended for one occurrence. If the action disrupts the study progress, such that the study design or outcome (endpoints) may be compromised, or the action compromises the safety and welfare of study subjects, advance documented IRB and DSMC approval is required.

- For exceptions on Industry or Cooperative group sponsored protocols, written approval must be obtained from the Sponsor prior to submitting the exception request to the DSMC.
- For in-house studies with a Medical Monitor or Safety Monitoring Committee (not DSMB), approval must be obtained from the Medical Monitor or Safety Monitoring Committee prior to submitting the exception request to the DSMC.

Deviation

A one time, unintentional action or process that departs from the IRB and DSMC approved study protocol, involving one incident and identified retrospectively, after the event occurred. If the impact on the protocol disrupts the study design, may affect the outcome (endpoints) or compromises the safety and welfare of the subjects, the deviation must be reported to the DSMC within 5 business days and the IRB within 10 business days.

Events Requiring Prompt Reporting to the IRB including Unanticipated Problem Involving Risks to Subjects or Others Reporting Requirements

Federal Regulation 21CFR §56.108(b)(1) and 45 CFR 46.103(b)(5) require the IRB to "follow written procedures for ensuring prompt reporting to the IRB…any unanticipated problems involving risk to human subjects or others."

In alignment with 21 CFR 312, investigators are required to promptly report to the IRB:

(1) Unanticipated problems including suspected adverse reactions and adverse reactions.

- An event is considered a "suspected adverse reaction" when there is reasonable possibility that the drug/investigational product caused the adverse event. For these reporting purposes, reasonable possibility means there is evidence to suggest a causal relationship between the drug/investigational product and the event.

- For University of Pennsylvania IRB reporting, this means an event should be considered probably or definitely related to the research procedures.

- An event is "unexpected" if it is not listed in the investigator's brochure/package insert, or, is not listed at the specificity or severity that has previously been observed with the specific drug/investigational product; if an investigator's brochure/package insert is not available, is not consistent with the risk information described in the general investigational plan.)

- "Unexpected" also refers to events that are mentioned in the investigator's brochure/package insert as occurring with a class of drugs or as anticipated, but, are not mentioned as to have been occurring (have been seen) with the particular drug/investigational product under study.

(2) Unanticipated adverse device reaction. Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

- For drug/investigational product and device events, "serious" is defined as any death, life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Other events that may be considered "serious" but not meet the prior criteria include: those events that may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes noted above.

(3) In addition to unanticipated problems, the IRB also requires prompt reporting of the following events:

- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.

- Violation or deviation (meaning an accidental or unintentional change to the IRB approved protocol) only when: one or more participants were placed at increased risk of harm, or, the event has the potential to occur again, the event represents serious or continuing noncompliance.

(4) Breach of confidentiality.

(5) Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
This study will be monitored in accordance with the DSMC monitoring plan. Dr. Dan Vogl will serve as medical monitor and will consult on decisions made as a part of this trial as noted above.

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

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for Pembrolizumab by 20% over the prescribed dose. No specific information is available on the treatment of overdose of Pembrolizumab. In the event of overdose, Pembrolizumab should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

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

8.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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. 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)

8.2.3 Immediate Reporting of Adverse Events to the Sponsor

8.2.3.1 Serious Adverse Events

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

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

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220 within two (2) business days of learning of the information.

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.

8.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 24 hours to Merck Global Safety.

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.

8.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI CTCAE, version 5.0. 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 8: Evaluating Adverse Events

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

V5.0 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.)

8.2.5 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.

8.2.6 Tumor Biopsies/Archival Tissue Collection

Provision of tissue from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion will be encouraged.

a. For archival tissue, 10 unstained slides of 4-5 micron thickness on positively charged slides are required.
b. Tumor tissue may be from a diagnostic biopsy or a portion of a surgical specimen, if surgery is a component of definitive intent therapy.
c. Formalin fixed paraffin embedded (FFPE) tissue samples are acceptable; a fine needle aspirate, frozen sample, plastic embedded sample, cell block, clot, bone, bone marrow or cytologic specimen will not be acceptable for IHC analysis.
d. It is recommended that FFPE blocks be sectioned fresh (within 7 days of sectioning and sending for PD-L1 analysis) onto positively charged slides; slides should be stored and shipped (and stored upon receipt at Qualtek) at 2-8C in the dark.
e. Recommended fixation time for samples is 24 hours to 48 hours in 10% neutral buffered formalin.

9 Statistical Plan

9.1 Statistical Analysis Plan Summary

The statistical analysis of the data obtained from this study will be the responsibility of the Biostatistics Core Facility of the Abramson Cancer Center.

Objectives of the study are stated in Section 3.

9.2 Sample Size Determination

The sample size will be 41 evaluable patients; i.e.: subjects who receive at least 1 dose of proton reirradiation.

9.3 Hypothesis/Evaluation

This phase II study evaluates a multi-stage treatment plan for recurrent disease that is comprised of definitive therapy consisting of proton reirradiation with or without chemotherapy, followed by consolidation Pembrolizumab, for recurrent NSCLC. A total of 41 patients will be enrolled on the study. Between the end of definitive therapy and the start of Pembrolizumab, there is a 4-12 week rest period. The primary intent-to-treat analysis will estimate PFS from start of definitive therapy, regardless of whether consolidation Pembrolizumab was administered. A secondary proof of principle analysis will estimate PFS in the subgroup of patients who receive definitive therapy followed by consolidation Pembrolizumab. The benefit of adding Pembrolizumab after definitive therapy will be determined in this analysis, by testing whether PFS is improved as compared to a historical control population who received standard therapy only. For this proof of principle analysis, the null hypothesis is that the median PFS from start of therapy for a recurrence of NSCLC is 6 months as compared to the alternative hypothesis that the median PFS is increased to 10 months.

9.3.1 Analysis Endpoints

Primary

Progression Free Survival (PFS) per RECIST 1.1

Progression Free Survival is defined as the time from initiation of definitive therapy to the first documented disease progression per RECIST 1.1 based on radiologists' review or death due to any cause, whichever occurs first, or last patient follow-up that documented lack of disease progression. Patients who have not had disease progression or who have died, will be censored on the most recent clinical evaluation date that documented that they were progression-free.

Secondary

Overall Survival

Overall Survival (OS) is defined as the time from initiation of definitive therapy to death due to any cause or last patient contact alive. Subjects without documented death at the time of the final analysis will be censored at the date of the last follow-up.

Toxicity Determination

Tolerability of therapy will be determined on the basis of CTCAE adverse event reporting. Toxicity will be reported separately for definitive therapy and Pembrolizumab. For the definitive therapy phase, we will report on adverse events which are grade 3 or higher treatment-related toxicities or any grade of pneumonitis or esophagitis. For the Pembrolizumab phase, we will report all treatment-related toxicities.

9.3.2 Efficacy Analysis Populations

The analysis of primary efficacy endpoints is based on the intention-to-treat (ITT) population. All patients who enroll will be included, regardless of whether they receive consolidation Pembrolizumab. A secondary efficacy analysis will be conducted that excludes those patients who did not initiate consolidation Pembrolizumab after definitive therapy. At least 25 treatments of radiation should be delivered in order to be included in the analysis.

9.3.3 Safety Analysis Populations

The All Patients as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all enrolled subjects who received at least one dose of study treatment. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of trial treatment is required for

inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

9.4 Statistical Methods

Primary Objective

1. The primary intent-to-treat analysis will estimate progression free survival from initiation of definitive therapy by the Kaplan-Meier method. Median PFS and 95% CI will be determined. A total of 41 patients will be enrolled on the study.
2. A secondary proof of principle analysis will determine the clinical benefit of adding consolidation Pembrolizumab after definitive therapy. Only patients who receive consolidation Pembrolizumab are included in this analysis. It is expected that up to 15% of enrolled patients will have progressive disease or lingering toxicity and will not start Pembrolizumab after definitive therapy. Thus we anticipate that at least 35 patients will be included.

   In this proof of principle analysis, we will compare progression free survival from initiation of definitive therapy to a historical control value. We assume the median PFS for the historical control population treated with standard therapy only is 6 months and the median PFS for the patients treated with definitive therapy and consolidation Pembrolizumab is 10 months. Assuming 35 patients are enrolled over 2 years and followed for an additional 3 months, the final analysis will have 80% power to detect an improvement in median PFS assuming exponential survival and 1-sided 5% significance level.

Secondary Objectives

1. Overall survival will be estimated by the Kaplan-Meier method. Median OS and 95% CI will be determined.
2. Toxicities will be graded, categorized and tabled. For the definitive therapy phase, we will report on adverse events which are grade 3 or higher treatment-related toxicities or any grade of pneumonitis or esophagitis. For the Pembrolizumab phase, we will report all treatment-related toxicities.

Exploratory Objective

1. Biomarkers will be tested for association with PFS using log rank test for categorical biomarkers and Cox proportional hazards regression for continuous biomarkers. Biomarkers will be tested for association with graded toxicity (i.e., worse toxicity grade) for specific categories of toxicity using chi square test for categorical biomarkers and Spearman's correlation for continuous biomarkers.

10 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

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

1. Name, address, telephone number and e-mail address;
2. Hospital or clinic address and telephone number;
3. Curriculum vitae or other summary of qualifications and credentials; and
4. Other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in this and other countries, including countries that do not have laws protecting such information.

Additionally, the investigator’s name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

10.2 Compliance with Financial Disclosure Requirements

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to discarding trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their

disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

10.5 Quality Management System

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

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided by the Sponsor.

11 Publication Plan

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases. However, manuscript submission timelines may be extended.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

Target meeting: ASCO annual meeting Spring 2018
Target final manuscript: Journal of Clinical Oncology Jul 01, 2018

12 Appendices

12.1 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.	

12.2 Common Terminology Criteria for Adverse Events V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI CTCAE version 5.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

12.3 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.

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