

**RADVAX™: A STRATIFIED PHASE I TRIAL OF PEMBROLIZUMAB
WITH HYPOFRACTIONATED RADIOTHERAPY IN PATIENTS WITH
ADVANCED AND METASTATIC CANCERS**

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1.0 TRIAL SUMMARY

Abbreviated Title	RadVax™: Pembrolizumab & Hypofractionated Radiotherapy
Phase	Phase I
Clinical Indication	Metastatic cancers
Trial Type	Phase I cohort with randomized expansion phase
Type of control	N/A
Route of administration	i.v.
Trial Blinding	N/A
Treatment Groups	2 radiotherapy cohorts; 5 disease cohorts
Number of trial subjects	70
Estimated duration of trial	2 years
Duration of Participation	3 months

IRB #: 821403

UPCC#: 40914

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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.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a Phase I cohort study of a fixed dose of Pembrolizumab in combination with two distinct regimens of hypofractionated radiotherapy. There will be five groups of patient diagnoses:

- Metastatic melanoma patients who have progressed while on PD-1 or PDL-1 therapy
- Metastatic NSCLC patients who have progressed while on PD-1 or PDL-1 therapy
- Metastatic & locally advanced pancreatic cancer patients
- Metastatic Breast cancer patients
- Other metastatic cancer patients

Pembrolizumab will be administered at a dose of 200 mg every 3 weeks beginning 7 days (+/- 3 days) prior to the first fraction of hypofractionated radiation and will continue for a total of 6 cycles. In the initial **Safety Phase**, there will be two cohorts of patients based upon the radiotherapy dose delivered to the index metastatic lesion in the lung, liver, bone or soft tissue:

Cohort 1: 8 Gy x 3 to the index lesion

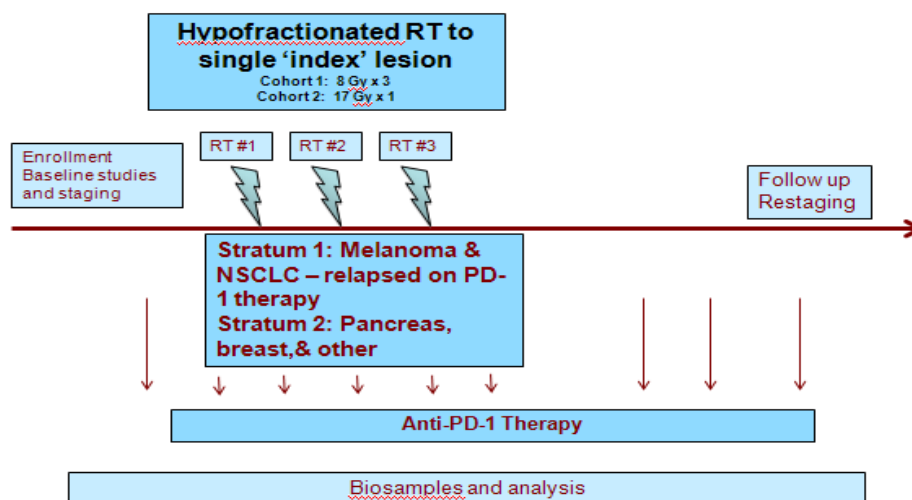
Cohort 2: 17 Gy x 1 to the index lesion*

*Subjects with locally advanced pancreatic cancer will be enrolled only in the 8 Gy x 3 cohort.

Patients are stratified by prior PD-1 therapy. 24 patients will be enrolled, 12 per stratum and 6 per fractionation cohort. Standard safety decision-making will be used. The regimen is safe if 0-1 dose-limiting toxicities (DLT) in 6 patients (3 from each strata). Enrollment in a cohort will stop if 2+ DLT are observed within a cohort at any time during the safety phase. If 2+ DLT are observed in Cohort 1, then Cohort 2 will still be tested. Cohort 1 → Cohort 2 is **not** an escalation of dose. DLT is defined as any Grade 3 or higher non-hematological toxicity and any Grade 4 hematological toxicity that is probably, possibly or definitely related to the combination of Pembrolizumab and hypofractionated radiotherapy. The window in which DLTs will be recorded is from the first Pembrolizumab infusion to 35 days after the last radiation fraction.

In the **Expansion Phase**, patients will be stratified by disease site. If both fractionation regimens are safe, then we randomize patients. Otherwise, all patients will be enrolled on the single regimen determined to be safe. 46 patients will be enrolled. Randomization will aid in the preliminary assessment of clinical response by avoiding selection bias. Accrual is expected to occur over 24 months or 3-4 subjects per month.

2.2 Trial Diagram



3.0 OBJECTIVE(S & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

- (1) **Objective:** To determine the safety of combining Pembrolizumab with hypofractionated radiotherapy in patients with advanced and metastatic cancers.

Hypothesis: Pembrolizumab will be safe and well tolerated in patients with advanced and metastatic cancers when combined with hypofractionated radiotherapy.

3.2 Secondary Objectives

Objective: To estimate the immune-related response rate in non-index metastatic lesions of the combination of Pembrolizumab and hypofractionated radiotherapy

3.3 Exploratory Objective

- (1) **Objective:** To explore the immune pharmacodynamic changes after treatment with the combination of Pembrolizumab and hypofractionated radiotherapy
- (2) **Objective:** To explore the relationship between PD-1 expression and response to Pembrolizumab and hypofractionated radiotherapy

4.0 BACKGROUND & RATIONALE

4.1 Background

Historically patients with metastatic disease from epithelial cancers have rarely been cured. The 5-year survival rates for patients diagnosed between 2004 and 2010 with

metastatic NSCLC, melanoma, and breast cancer are respectively 4%, 16%, and 25% (<http://seer.cancer.gov/statfacts/>). Pancreatic cancer, regardless of stage has a poor prognosis, with an overall survival rate of 6.7%. For patients with localized pancreatic cancer, survival is 25.8%, with regional disease 9.9% and with distant metastases 2.3%.

Hypofractionated radiotherapy for oligometastatic disease

Hypofractionated radiotherapy for metastatic disease is commonly delivered with stereotactic body radiotherapy (SBRT) in which several non-coplanar photon beams are used to treat a tumor with a high degree of conformality resulting in little dose to surrounding normal tissues. SBRT has proven to be an effective local treatment for small, localized tumors. Initially, it was integrated as an ablative approach with a goal of tumor sterilization in oligometastatic disease with minimal morbidity and good long-term clinical outcome in these highly selected patients (1-4). Our goal in this protocol is different; we propose to use is hypofractionated radiotherapy, either with or without an SBRT technique, to irradiate a single lesion in the setting of immune checkpoint blockade with the hope of augmenting a systemic response.

Immunologic approaches to treating patients with advanced stage cancer

Due to these poor survival rates, many different approaches have been tried for patients with advanced stage cancers. In particular, recent studies have shown benefit from immunotherapy. T lymphocytes are prime mediators of tumor immunosurveillance. Several immune checkpoint receptors are expressed on T cells that downregulate the activity of these cells after they have been activated. Hence, inhibition of these regulatory molecules is a means of augmenting anti-tumor response. Cytotoxic T-lymphocyte antigen-4 (CTLA-4; CD152) is a cell-surface receptor that is expressed (within approximately 72 hours *in vitro*) on T-lymphocytes in response to the activation by interaction with APCs or pharmacologic stimulation of the T-cell receptor (5). CTLA-4 activation downregulates T-cell proliferation and cytokine secretion, effectively limiting the immune reactivity directed against a given antigen stimulus. Therefore, inhibition of CTLA4 using an antibody is a potential strategy to prevent downregulation of the immune response. In 2010 Hodi *et al.* published the first phase III randomized trial demonstrating a survival benefit in patients with metastatic melanoma treated with ipilimumab, a fully human monoclonal antibody (IgG1) that blocks CTLA-4 (6). Based on this trial the drug was approved for use by the FDA in March 2011 for patients with metastatic melanoma.

Another immunomodulatory receptor that has garnered a great deal of attention is Programmed Death-1 (PD-1). PD-1 signaling involves binding to several discrete ligands, including PD-L1 and PD-L2. PD-L1 is often expressed within the tumor microenvironment by cancer cells and macrophages whereas PD-L2 is expressed primarily on professional antigen presenting cells (5). PD-1 negatively regulates the effector phase of the T cell response after ligation of PD-L1 to the receptor. Antibodies that block the PD-L1/PD-1 interaction prevent the downregulation of the anti-tumor immune response, hence augmenting the cytotoxic function of tumor-specific T cells.

Several PD-1 inhibitors have been used in large clinical trials. PEMBROLIZUMAB is a highly selective, humanized monoclonal antibody (IgG4) that blocks PD-1. Its safety and efficacy (response rate of 38% by RECIST criteria) have been demonstrated in melanoma (7). Another PD-1 inhibitor, BMS-936558, was found to be safe and to yield response rates (by RECIST) of 18%, 28%, 27% respectively in patients with advanced stage non-small lung cancer, melanoma and renal cell carcinoma (8).

Hypofractionated radiotherapy and immune activation

The effectiveness of the immunologic strategy outlined above is contingent upon T-lymphocyte activation through interaction with the APC having already occurred. Therefore, the development of novel strategies that successfully “vaccinate” patients to their cancer near the time of the delivery of the immunomodulatory antibody is an important area of clinical research. One means of potentially increasing exposure of T cells to tumor antigen is to expose the tumors to a few large fractions of radiation (hypofractionated radiotherapy).

There is emerging evidence that radiotherapy (RT) can stimulate the immune response, by a variety of mechanisms such as increasing TLR4 expression on dendritic cells, increasing priming of T cells in draining lymph nodes, and increasing tumor cell antigen presentation by dendritic cells (reviewed in (9)). Recently Verbrugge *et al.* showed that radiotherapy can enrich tumors of functionally active, tumor-specific effector cells (10). Lee *et al.* demonstrated that the therapeutic effect with ablative hypofractionated radiotherapy on local tumor control required activation of CD8+ T- lymphocytes (11).

Hypofractionated radiation has also been shown to potentiate systemic response to immunomodulatory therapy. A single large dose of RT increased the effects of Flt-3 ligand administration on distant pulmonary metastases, an effect that was only seen in immunocompetent C57Bl/6 mice, not immunodeficient nude mice (12). Hypofractionated radiation has also been shown to amplify immune response to traditional vaccines (13). Additionally, there are pre-clinical data to suggest that CTLA-4 blockade along with ablative radiotherapy to an index lesion can prevent the growth of a tumor outside the irradiated field (abscopal effect) through an immune-mediated effect (14).

In addition to these pre-clinical data, Postow *et al.* reported a patient with metastatic melanoma having progressive disease while on ipilimumab therapy who then underwent a course of hypofractionated RT to a painful paraspinal mass. The patient received a dose of ipilimumab two months after RT, and then had radiologic imaging two months after this, which showed radiologic regression of disease in the irradiated site as well as in regions outside the radiation fields (15).

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [2; 3; 4; 5; 6]. In particular, the presence of CD8+ T-cells and the ratio

of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [7; 8]. The structure of murine PD-1 has been resolved [9]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 ζ , PKC θ and ZAP70 which are involved in the CD3 T-cell signaling cascade [7; 10; 11; 12]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [13; 14]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, Tregs and Natural Killer cells [15; 16]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [17]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [18; 19; 20; 13]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [13]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL) [21]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

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

4.1.2 Preclinical and Clinical Trial Data

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

4.2 Rationale

Current RADVAX™ trial at Penn using hypofractionated RT and ipilimumab

Simulated by our own anecdotal report of a patient having progressive disease on immunomodulatory therapy who had a dramatic abscopal response to radiotherapy, we initiated a phase I/II trial at Penn to determine whether it would be safe to deliver ipilimumab following hypofractionated radiotherapy. Patients received either 2 or 3 fractions of radiotherapy, followed by 4 cycles of the anti-CTLA4 agent ipilimumab. By trial design patients were required to have at least two discrete metastatic lesions from melanoma, only one of which was irradiated.

The primary goal of the trial was to assess safety. To date 21 patients have been enrolled. Overall treatment was well tolerated with no deaths attributable to therapy and no grade 4 toxicities. The most common grade 3 toxicity was anemia. There were no dose-limiting toxicities (DLTs), which for this study was defined as any grade 4 or higher immune treatment-related toxicity or grade 3 or higher non-immune treatment (RT-related) toxicity. Fourteen patients completed the entire 4 cycles of ipilimumab (2 patients completed only 2 cycles and 2 patients only 3 cycles due to progressive disease; 2 patients received only 3 cycles due to the development of colitis).

The impact of the therapy on the irradiated lesion and the non-irradiated lesion(s) was evaluated using two standard modalities: (i) ^{18}F -2-deoxyfluoro-2-deoxyglucose (FDG) activity on positron emission tomography-computer tomography (PET-CT) as a measure of biological effects of therapy and (ii) CT imaging for Response Evaluation Criteria in Solid Tumors (RECIST 1.1) assessment. 19 patients have been followed long enough to evaluate radiologic response. Metabolic responses were observed by FDG-PET-CT in the irradiated (“index”) lesion in 9 out of 19 patients (47%) with 4 of these 9 patient showing a complete metabolic response (CMR) and 5 of the 9 showing a partial metabolic response (PMR). Of the remaining 10 patients, 7 did not have repeat PET imaging, and 3 had stable metabolic disease (SMD). For the lesions that were not irradiated, metabolic responses were seen in 4 patients (21%), of which 2 were CMR and 2 were PMR. Of the remaining 15 patients, 7 did not have repeat PET imaging, and 8 had progressive metabolic disease (PMD). Using RECIST criteria on non-irradiated lesions, 4 out of 19 patients (21%) had a partial response (PR), 2 patients had stable disease (SD), and 12 patients had progressive disease (PD). One patient did not have CT scanning performed to assess tumor response.

The median progression-free survival (PFS) is 4.9 months and the median overall survival (OS) 10.7 months. Ipilimumab alone resulted in a response rate of 10.9% in the study by Hodi *et al.* (6). In summary, the combination of ipilimumab with hypofractionated radiotherapy was safe without DLTs. However, ipilimumab-related side effects were significant and the combination of ipilimumab and RT showed modest improvement over what is reported in the literature. Although our study was not designed to assess response, the results do not show that the majority of the patients have significant shrinkage of their unirradiated lesions in response to radiation. The results of our Phase I study support the investigation of the anti-PD1 agent, Pembrolizumab, with radiation given its probable

superior toxicity profile compared to ipilimumab.

Preclinical Studies of RT and anti-PD1/PD-L1 therapy

RT has also been combined with inhibition of the PD1/PD-L1 pathway. *Deng et al.* found that PD-L1 was upregulated in the tumor microenvironment after radiation (16). Administration of anti-PD-L1 antibody enhanced the efficacy of RT through a cytotoxic T cell-dependent mechanism. Concomitant with tumor regression, RT and anti-PD-L1 synergistically reduced the local accumulation of tumor-infiltrating myeloid-derived suppressor cells (MDSCs), which suppress T cells and alter the tumor immune microenvironment.

Our own group at Penn has generated data using anti-PD1 therapy with RT. As noted above, emerging data indicate that optimal results will require combination therapies, of which radiation (RT) may hold promise. The effectiveness and mechanisms of action for this combination have not been well characterized, which potentially hinders efficient clinical translation. To address these issues, we have developed several pre-clinical mouse models for melanoma, breast cancer, and other cancer types to mechanistically dissect the combination of RT and immune checkpoint blockade. Using these models, we have determined that RT and immune checkpoint inhibitors such as anti-PD-1/PD-L1 cooperate to promote tumor response in both irradiated and unirradiated tumors (Minn, A personal communication). Survival and complete responses are significantly improved, and long-term anti-tumor immunity ensues. Using a series treatment resistant sublines that we derived combined with unbiased genome-wide and immune approaches, we have discovered mechanisms of resistance and druggable targets to inhibit resistance. Studies on immune mechanisms and biological effects of RT are providing insight into how combination therapy can work in non-redundant ways to improve response. Insight into immune mechanisms has also driven the discovery of potential blood-based biomarkers for response. In summary, by using pre-clinical models, our preclinical studies demonstrate that anti-PD1 therapy in combination with hypofractionated radiotherapy leads to significant responses in non-index (non-irradiated) lesions and therefore supports the proposed trial of Pembrolizumab with radiation. We plan to continue to address critical questions on which combinations are effective, what mechanisms of resistance might emerge, how resistance can be rationally targeted, and whether mechanistic insight can guide the development of biomarkers to predict response

4.2.1 Rationale for the Trial and Selected Subject Population

Anti-PD1 therapies have shown activity in melanoma and NSCLC (XX-ref). It is not clear if these agents will have activity in other diseases nor is it clear whether the immunostimulatory effect of hypofractionated radiotherapy in combination with these agents is cancer-specific or dependent upon single agent activity of the immunotherapeutic agent. Our preclinical data suggest that activity is observed in a broader range of tumor types. Therefore, we propose to study the safety and preliminary efficacy of the combination of Pembrolizumab and radiotherapy in five groups of patient diagnoses: melanoma, NSCLC, pancreatic cancer, breast cancer, and other. Our hypothesis is that safety will be established and that an exploratory analysis will demonstrate robust responses in all disease groups.

4.2.2 Rationale for Dose Selection/Regimen/Modification

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

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

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of 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 Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for PEMBROLIZUMAB in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). 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.

4.2.3 Rationale for Primary Endpoint

This is a Phase I study that will determine the safety of combining Pembrolizumab with hypofractionated radiotherapy. The absence of clinical data regarding the safety of this combination mandates the performance of a Phase I trial. The primary endpoint, therefore, will be the safe dose or doses of hypofractionated radiotherapy in combination with Pembrolizumab as defined by 0 or 1 DLTs observed in 6 patients within each radiation dose cohort.

4.2.3.1 Efficacy Endpoints

This is a Phase I study and therefore, efficacy will not be the primary endpoint. Nonetheless, we have designed the study to obtain an estimate of the immune-related response rate in non-index metastatic lesions of the combination of Pembrolizumab and hypofractionated radiotherapy (please see statistical section for greater detail).

4.2.3.2 Biomarker Research

While this is a Phase I study and not necessarily powered for extensive statistical evaluation of biomarkers, we will begin to directly test whether promising biomarkers exist for more in depth analysis. The focus on immune-related response rate in non-index metastatic lesions will be the basis for examining circulating immune responses for correlates of tumor response.

The main goals of these studies are to perform in-depth immune phenotyping and analysis of samples from humans treated with hypofractionated radiotherapy in combination with Pembrolizumab. Biosamples (blood and, where available, tumor) obtained from patients before and at serial time points during treatment will be analyzed. The primary goals for the basic studies with these human samples will be:

- High dimensional (15-17 color) flow cytometry to analyze T cell subsets (including naïve, effector, memory (effector memory and central memory), effector memory RA, exhausted, Th1, Treg and Tfh), co-expression of sets of multiple inhibitory receptors by relevant T cell subsets, transcription factor expression, and T comprehensive functional analysis (expression of cytokines, chemokines, cytotoxic molecules, and degranulation). These studies will focus on sophisticated immune phenotyping and defining correlates of response to hypofractionated radiotherapy in combination with Pembrolizumab. These studies will be performed on PBMC and, where available, TIL.
- Deep sequencing of the TCR will also be performed from blood and tumor as a novel way to interrogate tumor-specific T-cell responses induced by treatment. This method does not require a priori understanding of a particular tumor antigen or MHC. Of particular interest will be evidence of TCR clones increasing in the circulation after therapy that are also found in the patient's tumor. Such observations would be consistent with a "vaccine effect" of therapy and the persistence of these T cell clones over time may be a predictor of a durable response.
- Whole genome transcriptional profiling will be performed using PBMC and/or tumor to develop predictors of responses and to reveal underlying pathways. These studies will be integrated with findings from pre-clinical models to help define novel signatures of clinical responses.

Summary

Based on our own clinical data with RT and ipilimumab, and pre-clinical data from our group and in the literature, we propose a stratified phase I clinical trial of hypofractionated radiotherapy to an isolated index lesion in combination with the PD-1 inhibitor, Pembrolizumab in patients with metastatic cancers who have failed anti-PD-1 therapy (melanoma and NSCLC) and patients with metastatic cancers who have progressed after at least one regimen of systemic therapy (breast, pancreas, and other). In our protocol, the primary goal is to demonstrate that Pembrolizumab can be safely administered with hypofractionated radiotherapy. We will also estimate the immune-related response rate of non-index metastatic lesions.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

This is a cohort study of a fixed dose of Pembrolizumab in combination with two distinct regimens of hypofractionated radiotherapy. There will be five groups of patient diagnoses:

- Metastatic melanoma patients who have progressed while on PD-1 or PDL-1 therapy or have been on such therapy for at least 6 months with recent scan showing stable disease
- Metastatic NSCLC patients who have progressed while on PD-1 or PDL-1 therapy or have been on such therapy for at least 6 months with recent scan showing stable disease
- Metastatic & locally advanced pancreatic cancer patients
- Metastatic Breast cancer patients
- Other metastatic cancer patients

5.1.2 Subject Inclusion Criteria

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

1. Be willing and able to provide written informed consent/assent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Histologically confirmed diagnosis of cancer as per the cohort specifications
4. Stage IV cancer by AJCC staging criteria (except for pancreatic cancer cohort)
5. Locally advanced or metastatic pancreatic cancer for the pancreatic cancer cohort

6. Progression of disease while on anti-PD-1 or anti-PD-L1 therapy for melanoma and NSCLC patients. For this group, patients must met the following criteria:
 - a. Received at least 2 doses of an anti-PD1 or anti-PD-L1 therapy
 - b. Had progressive disease documented radiologically by RECIST v1.1 criteria.
7. Patients with metastatic melanoma or NSCLC who have been on anti-PD1 or anti-PD-L1 therapy for at least 6 months with a recent scan showing stable disease are also eligible.
8. Progression or refractory disease to at least one regimen of therapy for metastatic disease in the breast and pancreatic cancer cohorts
9. Presence of an index lesion ≥ 1 cm amenable to hypofractionated radiotherapy
10. Patients who have metastatic cancer must have at least one lesion that is outside the radiation field that measures greater than one cm that can be followed by RECIST 1.1. This lesion, if it is close to the radiated lesion, must receive no more than 10% of the dose prescribed to the target lesion.
11. Have provided tissue from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion.
12. Have a performance status of 0 or 1 on the ECOG Performance Scale.
13. Ability to tolerate hypofractionated radiation therapy (e.g. lie flat and hold position)
14. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 21 days of signing study consent.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	$\geq 1,500$ /mcL
Platelets	$\geq 100,000$ / mcL
Hemoglobin	≥ 9 g/dL or ≥ 5.6 mmol/L
Renal	
Serum creatinine OR Measured or calculated ^a creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤ 1.5 X upper limit of normal (ULN) OR ≥ 60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	

Serum total bilirubin	$\leq 1.5 \times \text{ULN}$ <u>OR</u>
	Direct bilirubin $\leq \text{ULN}$ for subjects with total bilirubin levels $> 1.5 \text{ ULN}$
AST (SGOT) and ALT (SGPT)	$\leq 2.5 \times \text{ULN}$ <u>OR</u> $\leq 5 \times \text{ULN}$ for subjects with liver metastases
^a Creatinine clearance should be calculated per institutional standard.	

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

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

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

5.1.3 Subject Exclusion Criteria

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

1. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.
2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. Systemic steroids administered specifically as a premedication for chemotherapy infusion or radiotherapy are allowed.
3. Has had a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e., \leq Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
4. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., \leq Grade 1 or at baseline) from adverse events due to a previously administered agent.

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

- Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
- 5. A history of prior radiotherapy that precludes delivery of hypofractionated radiotherapy
- 6. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
- 7. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment.
- 8. Has an 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 would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjogren's syndrome will not be excluded from the study.
- 9. Has evidence of interstitial lung disease or active, non-infectious pneumonitis.
- 10. Has an active infection requiring systemic therapy.
- 11. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
- 12. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
- 13. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
- 14. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
- 15. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

16. Has received a live vaccine within 30 days prior to the first dose of trial treatment.

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Tables 2 and 3

Table 2 Pembrolizumab Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Every 3 weeks	IV infusion	6 three week cycles*	Experimental
The PEMBROLIZUMAB dosing interval may be increased due to toxicity as described in Section 5.2.1.2.					

Pembrolizumab should be administered 7 days (+/- 3 days) prior to the first fraction of hypofractionated radiation.

*NOTE: Patients who have stable or responding disease and are felt to be clinically benefiting from the drug can continue receiving pembrolizumab for up to 2 years. For cancers not currently commercially approved for treatment with pembrolizumab, the drug will be provided by Merck.

In the initial **Safety Phase**, there will be two cohorts of patients based upon the radiotherapy dose delivered to the index metastatic lesion in the lung, liver, bone or soft tissue:

Cohort 1: 8 Gy x 3 to the index lesion

Cohort 2: 17 Gy x 1 to the index lesion*

*Subjects with locally advanced pancreatic cancer will be enrolled only in the 8 Gy x 3 cohort.

Patients are stratified by prior PD-1 therapy. 24 patients will be enrolled, 12 per stratum and 6 per fractionation cohort within each stratum. Standard safety decision-making will be used. The regimen is safe if no more than 0-1 dose-limiting toxicities (DLT) are observed in 6 patients within a cohort within a stratum. Enrollment in a cohort within a stratum will stop if 2+ DLT are observed within that cohort at any time during the safety phase. If 2+ DLT are observed in Cohort 1 in a stratum, then Cohort 2 within that stratum will still be tested. Cohort 1 → Cohort 2 is **not** an escalation of dose. DLT is defined as any Grade 3 or higher non-hematological toxicity and any Grade 4 hematological toxicity that is probably, possibly or definitely related to the combination of Pembrolizumab and hypofractionated radiotherapy.

Table 3. Hypofractionated Radiotherapy

Safety Phase:

Stratify		Cohort 1: 8 Gy x 3	Cohort 2: 17 Gy x 1	TOTAL
		Number of Patients	Number of Patients	
	Progressed on Prior PD-1 (Melanoma or NSCLC)	6	6	12
	No Prior PD-1 (Pancreas, Breast or Other)	6	6*	12
	TOTAL	12	12	24
* Breast or Other cancer patients only				

Expansion Phase

Disease	Randomize		Number of Randomized Patients
	Cohort 1: 8 Gy x 3 Number of Patients	Cohort 2: 17 Gy x 1 Number of Patients	
Melanoma	7	7	14
NSCLC	7	7	14
Pancreas	6	0	6*
Breast	3	3	6
Other	3	3	6

TOTAL	26	20	46
	* Pancreas patients are not randomized, they are assigned to 8 Gy x 3		

In the **Expansion Phase**, patients will be stratified by disease site. If both fractionation regimens are safe, then we randomize patients. Otherwise, all patients will be enrolled on the single regimen determined to be safe. We will proceed to the Expansion phase once 12 patients have been treated in a given stratum in the Safety phase and the requisite amount of time for observing DLTs has elapsed; i.e. once 12 patients have been treated in “No Prior PD-1 (Pancreas, Breast, Other)” stratum, patients can be enrolled on the Pancreas, Breast and Other strata in the Expansion phase. Likewise, once 12 patients have been treated in “Progressed on the Prior PD-1 (Melanoma, NSCLC)” stratum in the Safety phase and the requisite amount of time for observing DLTs has elapsed, patients can be enrolled on the Pancreas, Breast and Other strata in the Expansion phase.

46 patients will be enrolled. Randomization will aid in the preliminary assessment of clinical response by avoiding selection bias. Accrual is expected to occur over 24 months or 3-4 subjects per month.

Radiation Therapy

All subjects will be immobilized in a custom designed device in the appropriate position to isolate the index lesion. Radiotherapy treatment planning using CT or PET/CT scans (with contrast, unless contraindicated) will be required to define the gross target volume (GTV) and planning target volume (CTV). The treatment planning PET/CT scan should be acquired with the subject in the same position and using the same immobilization device as for treatment. Treatment planning will be done using a 3D based CT treatment planning system. All tissues to be irradiated must be included in the CT scan. Planning CT scan will be done at ≤ 5 mm intervals from encompassing the region of interest with sufficient margin for treatment planning.

Target Contouring

Gross Tumor Volume (GTV) is defined as all known gross disease encompassing the selected index lesion. The GTV will consist of the index lesion as visualized on CT and PET.

Internal Gross Tumor Volume (IGTV) is defined for mobile index lesions at the discretion of the treating physician. A 4-D CT scan may be acquired in order to account for the motion of the lesion during respiration. The IGTV will be defined as the union of the visualized index lesion on all gated CT data sets.

Planning Target Volume (PTV) will be defined as per the convention for photon beam radiotherapy. A 3-dimensional margin will be created on the GTV or IGTV (if available) to allow for daily set-up variance.

Normal Structures

Organ at risk volume (OAR) is contoured as visualized on the planning CT or MR scan. Planning PAR is the OAR expanded for setup uncertainty or organ motion. The physician will contour the OAR. The dosimetrist will create the PAR by expanding the OAR by 2-3 mm, depending on the situation.

Dose Fractionation and Specification

The prescription dose per fraction to the PTV will be 8 Gy x three fraction for Cohort 1 and 17 Gy per fraction x one fractions in Cohort 2. The total dose for Cohort 2 will be 24 Gy over 3 fractions.

Treatment Planning

Three-dimensional coplanar or non-coplanar beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. Non-opposing, noncoplanar beams are preferable.

Many of the patients on this trial will undergo SBRT. For these patients, standard protocols and constraints that have been developed in the Department of Radiation Oncology will be followed. For SBRT, typically, ≥ 10 beams of radiation will be used with roughly equal weighting. Generally, more beams are used for larger lesion sizes. When static beams are used, a minimum of 7 non-opposing beams should be used. For arc rotation techniques, a minimum of 340 degrees (cumulative for all beams) should be utilized. For arc rotation techniques, a minimum of 340 degrees (cumulative for all beams) should be utilized. In order to obtain acceptable coverage, field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view (i.e., no additional "margin" for dose buildup at the edges of the blocks or MLC jaws beyond the PTV). The only exception should be when observing the minimum field dimension of 3.5 cm when treating small lesions. As such, prescription lines covering the PTV will typically be the 60-90% line (where the maximum dose is 100%); however, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue.

Dose Selection/Modification

5.2.1.1 Dose Selection

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

Details on the dose preparation and administration are provided in the Merck Protocol, reference.

5.2.1.2 Dose Modification

PEMBROLIZUMAB will be withheld for drug-related Grade 3 or 4 hematologic toxicities (with the caveats as shown in Table 4 below) or Grade 3 or 4 non-hematological toxicity including laboratory abnormalities, and severe or life-threatening AEs.

Table 4: Dose modification guidelines for drug-related adverse events.

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with Sponsor)
Hematologic Toxicity	1, 2	No	N/A	N/A	N/A
	3* *Excluding Grade 3 neutropenia, anemia, and thrombocytopenia	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week	Toxicity does not resolve within 12 weeks of last infusion <i>Permanent discontinuation should be considered for any severe or life-threatening event</i>
	4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week	
Non-hematological toxicity	1	No	N/A	N/A	N/A
	2	Consider withholding for persistent symptoms	Toxicity resolves to Grade 0-1 or baseline	<i>Clinical AE resolves within 4 weeks:</i> Same dose and schedule (reference Section 5.6.1.2 for recommendations regarding pneumonitis) <i>Clinical AE does not resolve within 4 weeks:</i> May increase	Toxicity does not resolve within 12 weeks of last infusion

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with Sponsor)
For additional information regarding Adverse Events with a potential Immune-Etiology reference Section 5.6.1.1.				the dosing interval by 1 week for each occurrence	
	3, 4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last infusion <i>Permanent discontinuation should be considered for any severe or life-threatening event</i>

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued after consultation with the Sponsor. With investigator and Sponsor agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. For information on the management of adverse events, see Section 5.6.1.

Subjects who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of PEMBROLIZUMAB should be discontinued from trial treatment.

There will be no modification of radiotherapy.

5.2.2 Timing of Dose Administration

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

All trial treatments will be administered on an outpatient basis.

PEMBROLIZUMAB will be administered as a 30 minute IV infusion (treatment cycle intervals may be increased due to toxicity as described in Section 5.2.1.2). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Procedures Manual contains specific instructions for PEMBROLIZUMAB dose calculation, reconstitution, preparation of the infusion fluid, and administration.

5.2.3 Trial Blinding/Masking

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

5.3 Stratification and Randomization

During the Safety Phase of this study, patients will be stratified on the basis of having received prior immunotherapy (see Table 3). During the Expansion Phase, patients will be stratified by disease site. If both fractionation regimens are safe, then we will randomize patients. Otherwise, all patients will be enrolled on the single regimen determined to be safe. Randomization will aid in the preliminary assessment of clinical response by avoiding selection bias. The randomization procedure is described in the Statistical Section.

5.4 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the 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.

5.4.1 Acceptable Concomitant Medications

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

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant

medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.4.2 Prohibited Concomitant Medications

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

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than PEMBROLIZUMAB
- Additional Radiation therapy beyond that described in the radiotherapy section
 - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor.
- 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 to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

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

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

5.5 Rescue Medications & Supportive Care

5.5.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. These supportive care measures will be instituted for both Pembrolizumab and hypofractionated radiotherapy and include but not limited to the items outlined below:

- Diarrhea: 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). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.
 - In subjects with severe enterocolitis (Grade 3), PEMBROLIZUMAB will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.
 - In subjects with moderate enterocolitis (Grade 2), PEMBROLIZUMAB should be withheld and anti-diarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Regarding guidelines for continuing treatment with PEMBROLIZUMAB, see Section 5.2.
 - All subjects who experience diarrhea 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.
- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.
- Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.
- Immune-related adverse events: Please see Section 5.6.1.1 below and the separate guidance document in the administrative binder regarding diagnosis and management of adverse experiences of a potential immunologic etiology.
- Management of Infusion Reactions: Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension;

Hypotension; Myalgia (muscle pain); Nausea; Pruritis/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting.

Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of PEMBROLIZUMAB.

Table 5 Infusion Reaction Treatment Guidelines

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

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.	
<u>Grades 3 or 4</u> 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. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

5.5.1.1 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 is consistent with an immune phenomenon. irAEs may be predicted based on the nature of the PEMBROLIZUMAB compound, 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 and is included in the Event of Clinical Interest and Immune-Related Adverse Event Guidance Document located in the Administrative Binder. 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 6.

Table 6 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.

5.5.1.2 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 7.

Table 7 Recommended Approach to Handling Pneumonitis

Study drug associated	Withhold/Discontinue	Supportive Care
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pneumonitis	PEMBROLIZUMAB?	
Grade 1 (asymptomatic)	No action	Intervention not indicated
Grade 2	Withhold PEMBROLIZUMAB, may return to treatment if improves to Grade 1 or resolves within 12 weeks	Systemic corticosteroids are indicated. Taper if necessary.
Grade 3 and Grade 4	Discontinue PEMBROLIZUMAB	Systemic corticosteroids are indicated. The use of infliximab may be indicated as appropriate. Refer to the Event of Clinical Interest and Immune-related Adverse Event Guidance Document for additional recommendations.

For Grade 2 pneumonitis that improves to \leq 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 \geq Grade 2

Acute toxicities related to hypofractionated radiotherapy are mild (Grade I) and no treatment interruptions of radiotherapy are anticipated.

5.6 Diet/Activity/Other Considerations

5.6.1 Diet

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

5.6.2 Contraception

PEMBROLIZUMAB may have adverse effects on a fetus in utero. Furthermore, it is not known if PEMBROLIZUMAB has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥ 45

years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.2-Reporting of Pregnancy and Lactation to the Sponsor and to Merck

If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.6.3 Use in Pregnancy

5.6.4 If a subject inadvertently becomes pregnant while on treatment with PEMBROLIZUMAB, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 7.2.2.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.

5.7 Subject Withdrawal/Discontinuation Criteria

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

trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4 – Other Procedures. A subject must be discontinued from the trial for any of the following reasons:

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

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

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

- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of treatment with PEMBROLIZUMAB

Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop PEMBROLIZUMAB after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.2.1.

- Administrative reasons

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

5.8 Subject Replacement Strategy

Replacement of subjects will occur if the subject did not complete the course of therapy as defined as follows (unless they discontinue treatment because of a DLT).

Cohort 1: all 3 RT fractions and 3 of 6 Pembrolizumab doses, 1 before RT and 2 after RT

Cohort 2: 1 RT fraction and 3 of 6 Pembrolizumab doses, 1 before RT and 2 after RT

No subject can be replaced if they discontinue therapy as a result of DLT.

5.9 Clinical Criteria for Early Trial Termination

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

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

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

6.0 TRIAL FLOW CHART

Table 8

	Main Study Screening Visit	Pembrolizumab Administration, Cycles 1-6	Hypofractionated Radiotherapy	Post-radiation Safety visit	Post-Pembrolizumab Safety visit	Post-treatment Follow up visit
Scheduling Window	-28 to -1	Days 1, 22, 43, 64, 85, 106 ± 3 Treatment completion = Day 106	Cohort 1: Day 8 ± 3 Cohort 2: Days 8, 10 & 12 ± 3	30 days ± 7 post completion of radiotherapy	30 days ± 7 post treatment completion (Day 136)	Day 196 ± 14
Informed consent	X					
Eligibility checklist review	X					
Tests and Observations						
History and PE	X	X – Days 1, 22, 43, 64, 85, 106 ± 3	X	X	X	X
ECOG score	X	X – Days 1, 22, 43, 64, 85, 106 ± 3	X	X	X	X
¹⁸ F-FDG PET/CT and/or CT scan or	X (also needed)					

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MRI – baseline@	for treatment planning study prior to Day 8)					
¹⁸ F-FDG PET/CT and/or CT scan or MRI – restaging **		X – Day 64			X	X
Biopsy or Archival Tissue***	X					X
CBC	X*	X – Days 1, 22, 43, 64, 85, 106 ±3			X	X
Comp Metabolic Panel	X*	X – Days 1, 22, 43, 64, 85, 106 ±3			X	X
Pregnancy Test*	X					
Toxicity Assessment	X	X	X	X	X	X
Correlative studies (Five 10 ml green top tubes and one	X ^a	X ^b – Days 1, 22, 43, 85 ±3	X – Day 8		X	X ^c

5 ml SST tube)						
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X* - Measurements must be made within 21 days of signing study consent.

X@ - Imaging studies must be performed within 30 days \pm 3 of treatment initiation

** After radiological tumor assessment at screening, the first radiological assessment of tumor response status will be performed at day 64 (+/- 7 days), unless there is clinical indication warranting earlier radiologic imaging. If imaging at 64 days shows PD, treatment with pembrolizumab may continue until a repeat assessment 4-6 weeks later confirms PD. If this scan confirms progression of disease compared with previous scan that showed PD, then pembrolizumab should be discontinued.

Subsequent studies will be performed as per standard of care.

*** There is a potential for a second biopsy if patient is willing and has a lesion that is amenable.

^{a/b} The pre-treatment correlative studies sample can be drawn at either the main study screening visit or at Pembrolizumab infusion #1 (as long as the sample is drawn before the infusion takes place).

^c Additional blood samples may be obtained if patient requires additional radiation for palliation. This will at the discretion of the PI. This could take place even after patient has completed this trial. At most there would be 4 blood draws that could include pre-radiation samples, samples during the course of radiation, and samples 1-3 weeks after completion of radiation and then 5-7 weeks after completion of radiation.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

Study Visit Schedule

Days -28 to -1: Subject will be screened for enrollment in the study. After the subject is deemed potentially eligible for the study and consents, the subject will be seen in the outpatient radiation therapy and/or medical oncology clinics for a history, physical exam, baseline laboratory studies, correlative studies, scheduling of imaging studies (if needed), and scheduling of radiotherapy treatment planning and Pembrolizumab infusion. Radiotherapy treatment planning is a standard procedure and will consist of a simulation CT scan or ¹⁸F-FDG PET/CT or MRI scan as per the Department of Radiation Therapy standards. The simulation will be scheduled so that the subject may begin hypofractionated radiotherapy on Day 8 \pm 3

Day 1: Pembrolizumab infusion in medical oncology offices.

Day 8: Hypofractionated radiotherapy will be given in either three fractions of 8 Gy delivered on Days 8, 10 & 12 \pm 3 or, one fraction of 17 Gy delivered on day 8 \pm 3.

Days 1, 22, 43, 64, 85, 106 \pm 3: Pembrolizumab infusion in medical oncology offices. History, PE, ECOG assessment, correlative studies, and laboratory studies on Days 1, 22, 43, 64, 85, 106 \pm 3.

Day 38 or Day 42: Follow up safety visit with the radiation oncologist 30 days \pm 7 post completion of radiotherapy (Day 38 \pm 7 for Cohort 1 and Day 42 \pm 7 for Cohort 2). History, PE, and ECOG assessment,.

Day 106 \pm 7: Follow up safety visit with the radiation oncologist or medical oncologist 30 days \pm 7 post completion of the 6th cycle of Pembrolizumab. History, PE, ECOG assessment, laboratory studies, correlative studies, and imaging restaging will be performed at this visit.

Day 196: Follow up safety visit with the radiation oncologist or medical oncologist 90 days \pm 14 post the Day 136 safety visit. History, PE, ECOG assessment, laboratory studies, correlative studies, and imaging restaging will be performed at this visit.

Additional blood samples may be obtained if patient requires additional radiation for palliation. This will be at the discretion of the PI. This could take place even after patient has completed this trial. At most there would be 4 blood draws that could include pre-radiation samples, samples during the course of radiation, and samples 1-3 weeks after completion of radiation and then 5-7 weeks after completion of radiation.

Subject is considered off study following the completion of the Day 191 \pm 14 visit. Subjects will then be referred to the referring physician for subsequent follow up, according to standard of care. Every effort will be made to obtain records of subjects for post Day 191 follow up visits, and permission will be sought for the investigators to recontact the patient directly with regard to health status and toxicity.

*NOTE: Patients who have stable or responding disease and are felt to be clinically benefiting from the drug can continue receiving pembrolizumab for up to 2 years. For cancers not currently commercially approved for treatment with pembrolizumab, the drug will be provided by Merck.

7.1.1 Administrative Procedures

7.1.1.1. General Informed Consent

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

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

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

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

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

7.1.1.1 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.

7.1.1.2 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.

7.1.1.3 Prior and Concomitant Medications Review

Prior and concomitant medication review will be performed as part of the medical history described in 7.1.1.4

7.1.1.3.1 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.

7.1.1.3.2 Concomitant Medications

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

7.1.1.4 Disease Details and Treatments

7.1.1.4.1 Disease Details

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

7.1.1.4.2 Prior Treatment Details

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

7.1.1.4.3 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.

7.1.1.5 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 12.2). 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 hypofractionated radiotherapy and Pembrolizumab exposure or Pembrolizumab exposure alone should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irAE). See Section 5.6.1.1 and the separate guidance document in the administrative binder regarding the identification, evaluation and management of AEs of a potential immunological etiology.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.1.6 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,

7.1.1.7 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.

7.1.1.8 Vital Signs

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

7.1.1.9 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12.4) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart. After Cycle 8 assessment of ECOG status will be performed every other cycle in conjunction with the directed or full physical exam.

7.1.1.10 Tumor Imaging and Assessment of Disease

Imaging studies, typically a CT scan or an ^{18}F -FDG PET/CT scan will be performed as per institutional standards for the purposes of baseline tumor assessment, radiotherapy treatment planning, and restaging.

7.1.1.11 Tumor Tissue Collection and Correlative Studies Blood Sampling

Where available tumor tissue from tumor resections and/or biopsies will be analyzed by flow cytometry, TCR sequencing and/or transcriptional profiling as described in section 4.2.3.2. Sample availability including the number of cells obtained and the timing of tumor tissue availability relative to treatment will be considered in how the samples are analyzed. Our priorities will be: 1) flow cytometric analysis of TIL for T cell activation, exhaustion and reinvigoration as well as for PD-L1 expression; 2) TCR sequencing; 3) transcriptional profiling.

7.1.2 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 to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Procedures Manual.

7.1.2.1 Laboratory Safety Evaluations (Hematology, Chemistry)

Laboratory tests for hematology, chemistry, and others are specified in Table 9. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Procedures Manual.

Table 9 Laboratory Tests

Hematology	Chemistry		
Hematocrit	Albumin		
Hemoglobin	Alkaline phosphatase		
Platelet count	Alanine aminotransferase (ALT)		
WBC (total and differential)	Aspartate aminotransferase (AST)		
Red Blood Cell Count			
Absolute Neutrophil Count	Carbon Dioxide ‡ (CO ₂ or biocarbonate)		
	Calcium		
	Chloride		
	Glucose		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin (<i>If total bilirubin is elevated above the upper limit of normal</i>)		
	Total protein		
	Blood Urea Nitrogen		
‡ Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy			

Hematology	Chemistry		
test will be required. ‡ If considered standard of care in your region.			

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.3 Other Procedures

7.1.3.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be

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followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with PEMBROLIZUMAB may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.2.1. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

7.1.4 Visit Requirements

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

7.1.5. 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.

7.1.4.1 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and will be assessed by radiologic imaging as per clinical judgment of the Medical Oncologist to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with PEMBROLIZUMAB as detailed in Section 7.1.5.2.1. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with PEMBROLIZUMAB according to the criteria in Section 7.1.5.2.1 will move from the follow-up phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.2 – Trial Flow Chart for Retreatment.

7.1.4.1.1 Survival Follow-up

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

7.1.4.4.2 Tumor Response

To systematically characterize additional patterns of response in patients with metastatic cancer, Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 will be used. The details as to how RECIST criteria are applied are given below.

A maximum of 5 target lesions in total (and up to 2 per organ) can be identified at baseline and measured throughout the course of therapy. In order to be considered a measurable target lesion, a nodal lesion must be ≥ 1.5 cm in short axis diameter (SAD), and an extranodal lesion must be ≥ 1.0 cm in longest diameter (LD). The irradiated lesion will not be included as a target lesion for measurement using RECIST. The sum of diameters of the target lesions (SAD for nodal lesions and LD for extranodal lesions) is followed through the course of therapy.

Disappearance of all known lesions will be counted as complete response (CR). A reduction of at least 30% in the sum of the diameters of target lesions is defined as partial response (PR). Progressive disease (PD) is defined as $\geq 20\%$ increase in the sum of diameters of target lesions from nadir (including baseline if it is smallest sum). PD is also defined as unequivocal progression of existing non-target lesions that merits discontinuation of therapy.

7.1.4.4.3 Tumor Progression

If imaging at any time shows PD, treatment with pembrolizumab may continue until a repeat assessment 4-6 weeks later confirms PD. If this scan confirms progression of disease compared with previous scan that showed PD, then pembrolizumab should be discontinued. However, the [referring Medical Oncologist may remove the patient from the protocol after the first imaging showing PD](#). . It will be up to the patient's medical oncologist to determine the next course of therapy (if any). Further radiologic imaging will be obtained as per the referring physician's clinical judgment.

7.2 Assessing and Recording Adverse Events

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

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

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

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

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

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

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

For purposes of this trial, an overdose 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)

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

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

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

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

7.2.3.1 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 an other important medical event

Refer to Table 10 for additional details regarding each of the above criteria.

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

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

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

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

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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.

7.2.3.2 Events of Clinical Interest

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

Events of clinical interest for this trial include:

1. An overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

3. In the event a subject develops any of the following AEs, a detailed narrative of the event should be reported as an ECI to the Sponsor within 24 hours and to Merck Global Safety within 2 working days of the event:
 - a. Grade \geq 3 diarrhea
 - b. Grade \geq 3 colitis
 - c. Grade \geq 2 pneumonitis

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d. Grade \geq 3 hypo- or hyperthyroidism

A separate guidance document has been provided entitled “event of Clinical Interest and Immune-Related Adverse Event Guidance Document.” This document provides guidance regarding identification, evaluation and management of ECIs and irAEs. Additional ECIs are identified in this guidance document and also need to be reported to the Sponsor within 24 hours and to Merck Global Safety within 2 working days of the event.

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

ECIs that occur in any subject from the date of first dose through 90 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the Merck’s product, must be reported within 24 hours to the Sponsor and to Merck Global Safety within 2 working days.

7.2.4 Evaluating Adverse Events

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

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

Table 10 Evaluating Adverse Events

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

V4.0 CTCAE Grading	Grade 1	Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.
	Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
	Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.
	Grade 4	Life threatening consequences; urgent intervention indicated.
	Grade 5	Death related to AE
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	† Results in death ; or	
	† Is life threatening ; or places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	† Results in a persistent or significant disability/incapacity (substantial disruption of one’s ability to conduct normal life functions); or	
	† Results in or prolongs an existing inpatient hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	† Is a congenital anomaly/birth defect (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new cancer ; (that is not a condition of the study) or	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may	

	jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).						
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units						
Action taken	Did the adverse event cause the Merck product to be discontinued?						
Relationship to test drug	<p>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):</p> <table> <tr> <td>Exposure</td><td>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?</td></tr> <tr> <td>Time Course</td><td>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)?</td></tr> <tr> <td>Likely Cause</td><td>Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors</td></tr> </table>	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
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	<p>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</p>

		drug trial); or (4) Merck product(s) is/are only used one time.)
	Rechallenge	<p>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.</p>
	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.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

7.2.6 Investigator reporting: notifying the Penn IRB

This section describes the requirements for safety reporting by investigators who are Penn faculty, affiliated with a Penn research site, or otherwise responsible for safety reporting to the Penn IRB. The University of Pennsylvania IRB (Penn IRB) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Penn IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Penn IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

- Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

Unexpected (An event is “unexpected” when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

AND

Related to the research procedures (An event is “related to the research procedures” if in the opinion of the principal investigator or sponsor, the event was possibly, probably, or definitely caused by the research procedures.)

Reporting Process

Unanticipated problems posing risks to subjects or others as noted above will be reported to the Penn IRB using the form: “Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events” or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator’s study file.

Data Safety Monitoring Committee (DSMC) Reporting to the Abramson Cancer Center:

All related events regardless of expectedness will be submitted to the DSMC within 10 days. All grade 3 or higher events will be submitted to the DSMC within 5 days of knowledge.

All unexpected events regardless of attribution will be submitted to the DSMC within 10 days.

We will continue to send reports to the DSMC for 90 days following the last date the final subject received study treatment/therapy/intervention or was exposed to an investigational device. We will not send reports after the 90 day window.

All unexpected deaths or deaths related to the study agent(s)/device(s) will be reported within 24 hours. All other deaths will be reported within 30 days. Deaths of subjects off study for greater than 30 days from the last study intervention/treatment are not reportable except if the death is in house gene or cellular-therapies, deaths on in-house studies utilizing on-campus manufacturing of the study agent(s) or components of study agent(s) and deaths on first-in-human studies.

A deviation is 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.

Reporting Deaths: more rapid reporting requirements

Concerning deaths that occur during the course of a research study, the following describes the more rapid reporting requirement of the Penn IRB for specific situations:

- Report the event within 24 hours when the death is unforeseen (unexpected) and indicates participants or others are at increased risk of harm.
- Report the event within 72 hours, for all other deaths, regardless of whether the death is related to study participation.

For reportable deaths, the initial submission to the Penn IRB may be made by contacting the IRB Director or Associate Director. The AE/Unanticipated Problem Form is required as a follow up to the initial submission.

Other Reportable events:

For clinical drug trials, the following events are also reportable to the Penn IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.

- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
 - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
 - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
 - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- 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.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

7.3 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.0 STATISTICAL ANALYSIS PLAN

This is a stratified phase I trial with 2 phases: a safety phase and an expansion phase.

Safety Phase: Pembrolizumab is fixed. Two radiotherapy fractionation schedules are tested: 8 Gy x 3 and 17 Gy x 1. Patients are stratified by prior PD-1 therapy. 24 patients will be enrolled, 12 per stratum and 6 per fractionation cohort.

Table 11

		Cohort 1: 8 Gy x 3 Number of Patients	Cohort 2: 17 Gy x 1 Number of Patients	TOTAL
	Progressed on Prior PD-1 (Melanoma or NSCLC)	6	6	12

Stratify	No Prior PD-1 (Pancreas, Breast or Other cancers)	6	6*	12
	TOTAL	12	12	24
	* Breast or Other cancer patients only			

Safety Phase Decision-making: Dose limiting toxicity (DLT) is defined in Sections 2.1 and 5.2. The regimen is considered safe if 0-1 DLTs are observed in 6 patients within a stratum. Stop if 2+ DLT at any time. If 2+ DLT in Cohort 1, then Cohort 2 will still be tested. Cohort 1 → Cohort 2 is not an escalation of dose.

Expansion Phase: Patients are now stratified by disease site.

- If both fractionation regimens are considered safe for both prior PD-1 therapy strata, then we will randomize patients. Randomization will aid in our preliminary assessment of clinical response by avoiding selection bias. Although unlikely, if only one of the fractionation regimens is considered safe for both prior PD-1 therapy strata, then all patients will be enrolled on the fractionation regimen which was determined to be safe.

Table 12

Disease	Randomize		Number of Randomized Patients
	Cohort 1: 8 Gy x 3 Number of Patients	Cohort 2: 17 Gy x 1 Number of Patients	
Melanoma	7	7	14
NSCLC	7	7	14
Pancreas	6	0	6*
Breast	3	3	6
Other cancers	3	3	6
TOTAL	26	20	46
	* Pancreas patients are not randomized, they are assigned to 8 Gy x 3		

Expansion Phase Decision-making: We will first evaluate response rate by fractionation cohort. We will pool all disease sites. This is a global assessment of RADVAX™ by fractionation cohort. Of 38 patients in cohort 1, 26 (68%) and of 32 patients in cohort 2, 20 (63%) will have been randomized to treatment in the expansion phase, which strengthens any comparative conclusions, although preliminary. Immune PD markers will also be examined by fractionation cohort.

Table 13

	Cohort 1: 8 Gy x 3 Number of Patients	Cohort 2: 17 Gy x 1 Number of Patients	STUDY TOTAL
Safety phase	12	12	24
Expansion phase	26	20	46
TOTAL	38	32	70

The following are examples of response rates and exact 95% CIs based on 38 patients in Cohort 1 and 32 patients in Cohort 2.

Table 14

<u>Cohort 1</u>			<u>Cohort 2</u>		
<u>N= 38 patients</u>			<u>N = 32 patients</u>		
<u># Respond</u>	<u>Response Rate</u>	<u>95% exact CI</u>	<u># Respond</u>	<u>Response Rate</u>	<u>95% exact CI</u>
<u>5</u>	<u>13.2%</u>	<u>4.4 – 28.1%</u>	<u>4</u>	<u>12.5%</u>	<u>3.5 – 29.0</u>
<u>10</u>	<u>26.3%</u>	<u>13.4 – 43.1%</u>	<u>8</u>	<u>25.0%</u>	<u>11.5 – 43.4</u>
<u>19</u>	<u>50.0%</u>	<u>33.4 – 66.6%</u>	<u>16</u>	<u>50.0%</u>	<u>31.9 – 68.1</u>
<u>30</u>	<u>78.9%</u>	<u>62.7 – 90.4%</u>	<u>24</u>	<u>75.0%</u>	<u>56.6 – 88.5</u>
<u>35</u>	<u>92.1%</u>	<u>78.6 – 98.3%</u>	<u>28</u>	<u>87.5%</u>	<u>71.0 – 96.5</u>

Next we will evaluate response rate by disease site. Here we pool fractionation cohorts. This is an assessment of RADVAX™ activity by disease, although preliminary.

Table 15

Disease	Safety Phase (Number is expected not required ^{**})	Expansion Phase (Number is required)	STUDY TOTAL
Melanoma	6	14	20
NSCLC	6	14	20
Pancreas	4	6	10
Breast	4	6	10
Other cancers	4	6	10
^{**} assumes equal numbers by disease strata in (12 prior PD-1 and 12 no prior PD-1			

For Melanoma and NSCLC cohorts: If 0/14 in the expansion phase respond then we can rule out a 20% response rate with 95% confidence. If 0/20 (pooling both phases) respond, then we can rule out a 15% response rate with 95% confidence.

For Pancreas, breast cancer and other cancers: If 0/6 in the expansion phase respond then we can rule out a 40% response rate with 95% confidence. If 0/10 (pooling both phases) respond, then we can rule out a 27% response rate with 95% confidence.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by Merck as summarized in Table 16.

Table 16 Product Description

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

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

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

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Compliance with Trial Registration and Results Posting Requirements

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

11.0 DATA HANDLING AND RECORD KEEPING

11.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

11.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

11.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. **DO NOT ERASE OR WHITE OUT ERRORS.** For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

11.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

12.0 ETHICAL CONSIDERATIONS

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.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See attachment for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the

EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject, and the investigator-designated research professional obtaining the consent.

13.0 STUDY FINANCES

13.1 Funding Source

This study will be supported with funds from Merck, Inc. and internal funds from the Department of Radiation Oncology.

13.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the University conflict of interest policy.

14.0 PUBLICATION PLAN

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study. Rule regarding the publication of results from this study are covered in the sponsored research agreement between Merck and the University of Pennsylvania.

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17.0 APPENDICES

17.1 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.	

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

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

17.3 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.

17.4 Pembrolizumab Event of Clinical Interest Guidance Document