TITLE: A Pilot Study to Assess the Combination of High-Dose Conformal Radiation Therapy (HDCRT) and Pembrolizumab in Modulating Local and Systemic T-cell Responses in Advanced Malignancies

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SIGNATURE PAGE

Sponsor-Investigator		
_____	_____	_____
Name	**Signature**	**Date**

INVESTIGATOR'S AGREEMENT

I confirm that I have read this protocol and I agree to conduct the study as outlined herein. I agree to conduct the study in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices, as outlined in ICH E6, and the applicable laws and regulations.

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1.0 TRIAL SUMMARY

Abbreviated Title	HDCRT Plus Pembrolizumab in Solid Tumors
Trial Phase	Pilot
Clinical Indication	Solid tumors when palliative HDCRT is indicated
Trial Type	Open-label
Type of control	N/A
Route of administration	Pembrolizumab (intravenous)
Trial Blinding	N/A
Treatment Groups	HDCRT plus pembrolizumab Arm A: HDCRT administered with first dose of pembrolizumab Arm B: HDCRT administered between doses 1 and 2 of pembrolizumab Arm C: HDCRT administered prior to first dose of pembrolizumab Please refer to study schema (Figure 1)
Number of trial subjects	Maximum sample size of 21 subjects
Estimated enrollment period	2 years
Estimated duration of trial	4 years
Duration of Participation	up to 2 years Subjects will receive 4 doses of pembrolizumab over the course of 12 weeks. Those subjects who have measurable disease (based on RECIST 1.1) outside of the radiation field and who have derived benefit from pembrolizumab may receive up to 2 years of pembrolizumab.
Estimated average length of treatment per patient	About 1 year

2.0 TRIAL DESIGN

2.1 Trial Design

This study is an open-label, pilot study of high-dose conformal radiation therapy (HDCRT) administered in combination with pembrolizumab (Figure 1). The study will accrue up to 21 subjects.

HDCRT
HDCRT will be administered to the primary tumor and/or sites of metastatic disease (1 or more sites permitted) over a period of 3-5 days. The length of time for administration of the HDCRT will depend on the site of disease that is to be radiated. HDCRT will begin on day 1 for Arms A and C and will begin on day 22 for Arm B. For

lesions that have not been previously radiated, HDCRT will be administered at a constant dose for sites of tumor involvement: 24 Gy in 3 fractions of 8 Gy each for bone and/or soft tissue lesions; 30 Gy in 5 fractions of 6 Gy each for the prostate gland.

Pembrolizumab

All study subjects will receive pembrolizumab (200 mg).

Groups A and B: Pembrolizumab will be administered on days 1, 43, 64, and 85. Subjects who have measurable disease (based on RECIST 1.1) outside of the radiation field and who have derived benefit from the 4 doses of pembrolizumab may continue to receive pembrolizumab every 3 weeks for up to 2 years.

Group C: Pembrolizumab will be administered on days 22, 43, 64, and 85. Subjects who have measurable disease (based on RECIST 1.1) outside of the radiation field and who have derived benefit from the four doses of pembrolizumab may continue to receive pembrolizumab every 3 weeks for up to 2 years.

Biopsies

All subjects will undergo 2-3 biopsies:

Day 1: Required only if a pre-study biopsy is not available or if a subject has received prior radiation at a tumor site and will be re-radiated at that tumor site as part of the proposed study. The pre-study biopsy may be obtained up to 6 weeks prior to initiation of treatment on Day 1. There should be no intervening treatment in between the pre-study biopsy and Day 1.

Days 22 and 43: Required on at least one HDCRT-treated lesion. Biopsies will also be completed on other unirradiated lesions, if feasible.

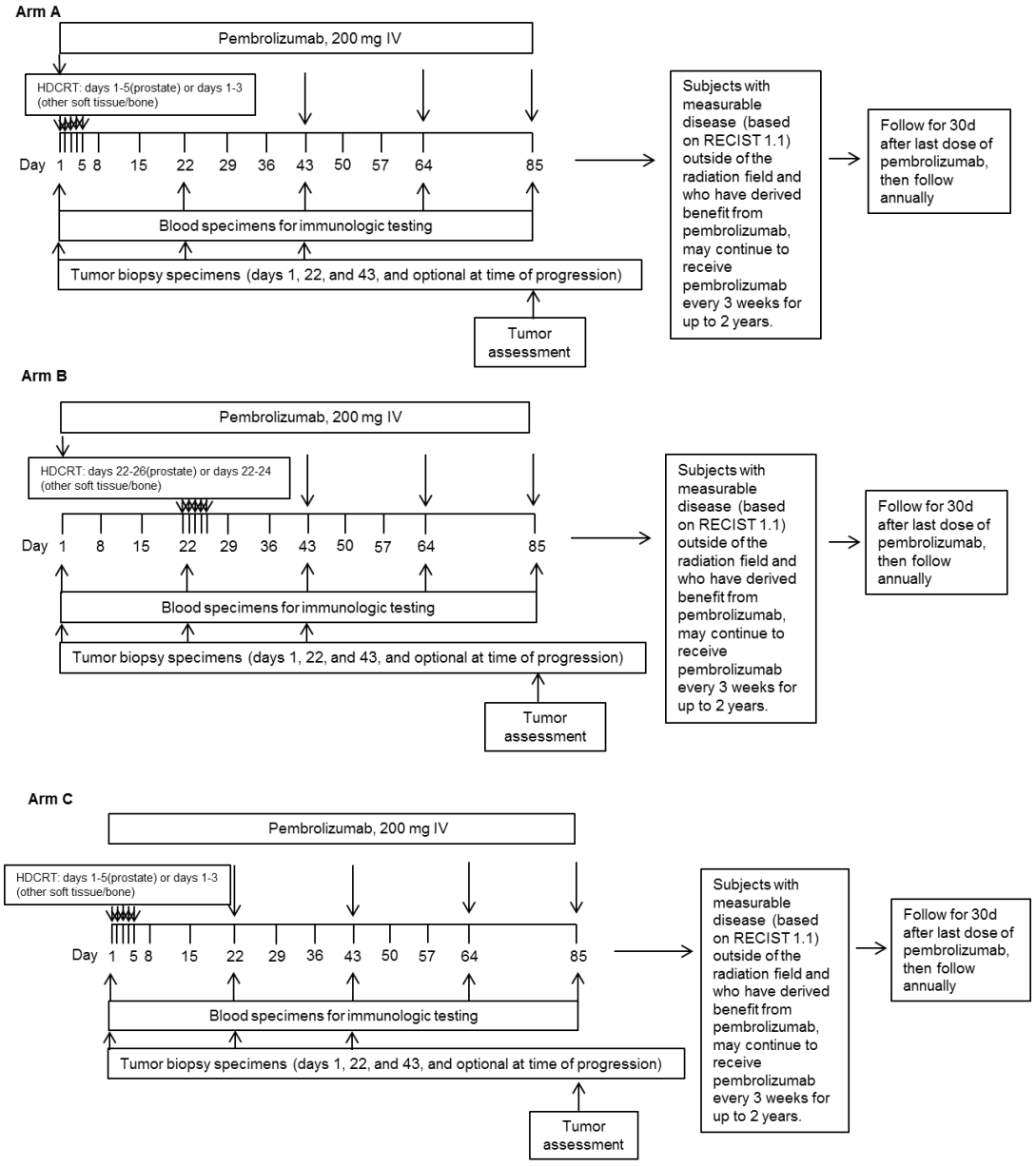
Research Bloods

All participants will have blood collected for immunologic assessments throughout the course of the study. Assessments will include evaluations of T cell frequency, phenotype and function.

Tumor Assessments:

The study is not powered for differences in clinical outcome, but we will track clinical responses and overall survival. Tumor assessments will be completed at screening, Day 85, and then per standard clinical practice based on tumor site, or a minimum of every 12 weeks.

Figure 1: Trial Diagram



3.0 OBJECTIVE(S)

3.1 Primary Objective(s)

1) Safety Objective
   - Obtain preliminary data on the safety of HDCRT with immunotherapy, delivered concurrently (Arm A) or sequentially (Arms B & C).

2) Immunologic Objective
   - Estimate the effect of HDCRT, pembrolizumab and the combination of HDCRT and pembrolizumab on $CD8^+$ T cell and $CD4^+$ T regulatory cell (T_{reg}) infiltration in tumors.

3.2 Secondary Objective

- Estimate the effect of HDCRT, pembrolizumab, and the combination of HDCRT and pembrolizumab on the lymphocyte composition of blood over time.

3.3 Exploratory Objectives

- Describe the effect of HDCRT, pembrolizumab and the combination of HDCRT and pembrolizumab on $CD8^+$ T cell and T regulatory cell (T_{reg}) infiltration in unirradiated tumors when available.
- Describe changes in serum biomarkers when available (e.g. prostate-specific antigen) and changes in tumor dimensions for unirradiated tumor lesions.
- Describe changes in activation markers on T cells in the blood (e.g. HLA-DR).
- Describe changes in the representation or frequency of T-cell receptor (TCR) sequences derived from: a) tumor infiltrating lymphocytes and b) tumor specific T cells in the blood.
- Describe associations/cross classifications between change in $CD8^+$ T cell and T regulatory cell (T_{reg}) infiltration in tumors.
- Summarize clinical outcomes of response, progression-free survival and overall survival

4.0 BACKGROUND & RATIONALE

4.1 Background

The immune system is known to play a fundamental role in the recognition and eradication of tumors. Over the past few decades immune-based therapies have been explored as treatment options for multiple cancer types. These immune-based therapies have included peptide and protein-based vaccines, cell-based vaccines, cytokine therapies, small molecular inhibitors, and antibody therapies directed at tumor specific antigens and immune cells (1,2). Recently, checkpoint inhibitors, antibodies that target regulatory cell-surface proteins on T cells, have been evaluated for clinical efficacy. One checkpoint inhibitor in particular, anti-PD-1, has demonstrated clinical benefit in melanoma and lung cancer, and is currently undergoing rigorous evaluation in other cancer types (3,4).

Despite the effectiveness of available immunotherapeutic approaches, current immune therapies still fail in a large proportion of patients. Thus, there is a need for new combination approaches that build on the demonstrated clinical value of immune therapy alone. Combination therapies designed to increase the tumor-derived antigen pool and enhance T cell infiltration into the tumor microenvironment, may directly impact the clinical benefit currently seen with single-agent immune therapies, such as anti-PD-1 therapy.

4.2 High-dose Conformal Radiation Therapy (HDCRT) in the Treatment of Primary and Metastatic Disease

In 1995, Hellman and Weichselbaum proposed that tumors begin in an oligometastatic state, with one or few metastases present (5). Localized treatment of oligometstases using ablative therapies such as HDCRT can be effective in eliminating tumor, and long-term clinical benefit can be achieved by preventing the outgrowth of tumor cell variants with increased metastatic potential (6). Interest in utilizing HDCRT for the treatment of metastatic cancer has increased following reports of the abscopal effects associated with radiation therapy (7). Observed clinical responses of tumors outside of the irradiated volume suggest that HDCRT may improve systemic responses to treatment through an immune-mediated process, although the effects of HDCRT on systemic immune-specific tumor control are still under investigation (7-9). Pre-clinical models have provided the framework for studying and characterizing the immunobiology of tumors and the tumor microenvironment following treatment with HDCRT.

4.2.1 Preclinical Data Evaluating the Effects of HDCRT on Tumor Specific Immune Responses

The capacity of an activated adaptive immune response to control a variety of tumors has been demonstrated in murine models and in recent clinical trials (10). However, while it is clear that many patients make spontaneous responses to their tumors, these responses typically are insufficient in controlling tumor outgrowth. This is due in part to the inability of immune cells to access or persist in the tumor microenvironment (TME) (11).

Recent studies with mouse transplantable tumor models have shown that irradiation and selected chemotherapeutic agents can induce a form of apoptosis termed immunogenic cell death (ICD). ICD is characterized by the release of chemotactic factors including ATP, CXCL9, -10, -11 and CXCL16; the translocation of calreticulin to the cell surface, and the elaboration of damage associated molecular patterns (DAMPs) including HMBG1 and heat shock proteins (12). In concert, these signals recruit antigen-presenting cells (APC) to the tumor microenvironment where APC can phagocytose tumor cells and associated debris. The signals from ICD further induce maturation of APCs, which primes the APC for the activation of naive T cells. Approaches that induce ICD, therefore, have the potential to induce trafficking of immune cells to sites of tumor and allow for auto-vaccination against tumor-derived antigens.

In murine models of metastatic lung and prostate cancer, preliminary data have shown that irradiation of primary tumor induces dendritic cell (DC) infiltration, promotes presentation of tumor antigens, activates systemic, anti-tumoral humoral and T cell immunity, and improves survival by eradicating metastases (13,14). In a preclinical model of prostate cancer, stereotactic body radiation therapy (SBRT) augments both the magnitude of the $CD8^+$

response to a recombinant listeria vaccine, and the ability of vaccine-induced cells to infiltrate primary tumors (14). However, it is clear that in many cases, the initiation of ICD in the tumor does not sufficiently drive immune responses to a level that can consistently control tumors. In part, this may be due to the relatively weak stimuli provided by ICD (in comparison to pathogen derived molecules). Further, multiple barriers, including regulatory T cell populations and the expression of molecules that suppress T cell function may remain at the tumor site following radiation therapy. These barriers may in part, be overcome by combining HDCRT with immune modulators, such as pembrolizumab, that can activate and sustain tumor-specific responses.

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

4.3.1 Pharmaceutical and Therapeutic Background

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

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

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

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

4.3.2 Preclinical and Clinical Trial Data for Pembrolizumab

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

4.4 Rationale

4.4.1 Rationale for the Trial and Selected Subject Population

This is a pilot study with primary endpoints to evaluate safety and immunologic parameters of the combination of HDCRT with pembrolizumab. We have selected to include patients with solid tumors for which palliative radiation is indicated as part of clinical care, and whose disease has progressed after receiving at least one standard systemic therapy and who have no other curative therapies available.

Tumor control by HDCRT is thought to be mediated in part by the induction of immunologic changes within the tumor microenvironment; however, structural barriers within the tumor and the expression of inhibitor molecules by tumor cells and surrounding tissue may impede HDCRT-induced immune-mediated control. Pembrolizumab is a checkpoint blockade inhibitor that blocks T cell inhibition and induces clinical responses in multiple tumor types. Combining HDCRT with pembrolizumab may lead to enhanced tumor control through the induction of tumor specific immune-mediated processes. This study aims to develop a platform for characterizing the immunobiology of the tumor and the tumor microenvironment, following administration of HDCRT and pembrolizumab, and in determining whether the sequence of administration of HDCRT and pembrolizumab impacts the development of the immune response against the tumor.

4.4.2 Rationale for Dose Selection/Regimen/Modification

HDCRT-Lesions that have not been previously radiated

For all sites of disease, other than the prostate gland, a dose schedule of 24 Gy in 3 fractions will be used This dose fractionation schedule is consistent with the UVA Department of Radiation Oncology's experience with short course radiation therapy for

palliative treatments and is also a dose that has been shown to produce synergy with immunotherapeutic approaches (15,16).

For the prostate gland, subjects will receive a dose of 30 Gy in 5 fractions. This dose is slightly lower than the dose of 36.25 Gy used in contemporary clinical trials of definitive SBRT for localized prostate cancer, such as Radiation Therapy Oncology Group 0938. This dose selection reflects ongoing concerns about the long-term safety of prostate SBRT at the higher doses used for definitive treatment of localized prostate cancer. The dose schedule of 30 Gy in 5 fractions is also the dose schedule currently used at UVA for patients with metastatic prostate cancer who receive primary prostate gland radiation therapy.

HDCRT-previously radiated lesions

For previously radiated lesions, HDCRT will be administered at 25 Gy in 5 fractions.

Pembrolizumab

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475 (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 MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

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

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between

the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

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

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

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

4.4.3 Rationale for Endpoints

4.4.3.1 Biomarker Research

We hypothesize that administration of the combination of HDCRT and pembrolizumab will augment T cell infiltration into sites of primary and/or metastatic tumor lesions, and that the phenotype and functionality of the infiltrating T cell subsets will favor the induction of enhanced immunologic responses against tumor. The following immunologic assessments are included to evaluate our hypothesis:

Immunohistochemistry

Tissue microarrays (TMAs) will be probed by immunohistochemistry(IHC) for alterations in the frequency and differentiation of $CD8^+$ T cells, $CD4^+$ T cells, NK cells and myeloid cells (including dendritic cells (DC), myeloid-derived suppressor cells (MDSC), and tumor associated macrophages (TAM). Furthermore, PD-L1 expression will be determined.

T-cell Receptor Sequencing

Formalin-fixed tissues and PBMC will be evaluated by T-cell receptor (TCR) sequencing by Adaptive Biotechnologies (Seattle, WA). TCR sequences from irradiated tumors will be compared with those from PBMC and unirradiated tumors (when available) for sequence frequency and diversity.

Gene Expression Analysis

Tumor-derived mRNA will be evaluated by QT-PCR for a panel of cytokines and chemokines representative of an inflammatory immunological signature (e.g. CXCL-9, -10, -11, IFN-γ).

Flow Cytometry

Single-cell suspensions derived from tumor biopsies and peripheral blood will be phenotyped by flow cytometry. In particular, the expression of activation markers, regulatory proteins and cellular subsets will be evaluated pre- and post-irradiation.

Cytokine Bead Array

The presence of inflammatory and regulatory cytokines will be determined in supernatants derived from tumor biopsies.

4.4.3.2 Efficacy Endpoints

The primary endpoints of the study are to evaluate the safety and immunologic effects of the administration of HDCRT with pembrolizumab. As part of the exploratory objectives, we will summarize clinical outcomes of response in those subjects who have measurable disease outside of the radiation field, progression-free survival, and overall survival. RECIST 1.1 will be used as the primary measure for clinical response. Subjects with progressive disease may undergo a second scan at least 4 weeks later to confirm progression and exclude the possibility of a tumor flare reaction, according to immune-related response criteria (irRC) guidelines. Criteria for continuing treatment after initial radiologic progression are provided in Section 5.8.1.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Subjects must have a histologically or cytologically proven advanced solid tumor malignancy for which palliative radiation is recommended. In solid tumors where pembrolizumab has been approved for use, patients may receive pembrolizumab as indicated, in the context of this protocol. In solid tumors where pembrolizumab has not been approved for use, the following criteria apply:

- Patients must be resistant to at least 1 prior conventional chemotherapy regimen or other standard of care regimen,
- Patient must have no remaining conventional treatment options proven to provide long-term disease control, and
- Patient has declined other conventional treatment options

Palliative radiation therapy may be recommended for primary tumor and/or any metastatic site that is accessible to biopsy.

Subject Inclusion Criteria

1. Subjects must be willing and able to provide written informed consent/assent for the trial.

2. Subjects must be ≥ 18 years of age on day of signing informed consent.

3. Subjects must have a least one site of disease that is accessible to radiation and multiple biopsies. Subjects may have disease that is encompassed within the radiation field or may have known disease both inside and outside of the radiation field.

4. Subjects must be able to provide tissue from 2-3 separate biopsy procedures that will be completed throughout the course of the study.

   a. Day 1 biopsy: Required only if a pre-study biopsy is not available or if a subject has received prior radiation at a tumor site and will be re-radiated at that tumor site as part of the proposed study. The pre-study biopsy may be obtained up to 6 weeks prior to initiation of treatment on Day 1. There should be no intervening treatment in between the pre-study biopsy and Day 1.

   b. Day 22 biopsy: Required.

   c. Day 43 biopsy: Required.

5. Subjects must have a performance status of 0, 1 or 2 on the ECOG Performance Scale.

6. Subjects must demonstrate adequate organ function as defined in Table 1.

Table 1: Adequate Organ Function Laboratory Values

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

	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

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

8. Female subjects of childbearing potential (Section 5.7.2) must be willing to use an adequate method of contraception as outlined in section 5.8.2-Contraception, for the course of the study through 120 days after the last dose of study medication.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

9. Male subjects of childbearing potential (Section 5.7.2) must agree to use an adequate method of contraception as outlined in Section 5.7.2-Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

10. Subjects must have a life expectancy ≥ 6 months

5.1.2 Subject Exclusion Criteria

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

1) Requires urgent treatment with cytotoxic chemotherapy or other therapy is indicated (e.g., symptomatic visceral metastases).

2) Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of Day 1.

3) Has a diagnosis of immunodeficiency.

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

5) Has hypersensitivity to pembrolizumab or any of its excipients.

6) Has received the following at study entry or within 4 weeks prior to study Day 1 or has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier:

   - Prior anti-cancer monoclonal antibody (mAb), including anti-PD-1, anti-PD-L1 and anti-PD-L2 blockade
   - Any growth factors (e.g. GM-CSF, G-CSF, erythropoietin).
   - Interferon or interleukin therapy.
   - Other Agents with putative immunomodulating activity.

7) Has received the following within 7 days prior to study Day 1:
   - Allergy desensitization injections
   - Systemic corticosteroids of more than 10 mg per day of prednisone (or equivalent), and administered parenterally or orally, except for physiologic replacement. Inhaled steroids (e.g. Advair®, Flovent®, Azmacort®) are not permitted. Topical corticosteroids are acceptable, including steroids with very low solubility administered nasally for local effects only (e.g. Nasonex®).

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

   - Note: Subjects with alopecia or ≤ 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.

   - Note: Lesions that have been selected for HDCRT may have been previously radiated provided:

     i. The tumor site that was previously radiated has progressed.

     ii. A baseline biopsy of the tumor site is obtained following progression and prior to study entry.

     iii. The lesions can be treated with 25 Gy in 5 fractions per the discretion of the treating radiation oncologist.

- Note: Subjects currently receiving androgen deprivation therapy or hormonal therapy are allowed.

- Note: Subjects receiving nitrosureas within 6 weeks prior to study Day 1 are excluded.

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

10) Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with untreated brain metastases and patients who have had brain metastases re-treated with radiation will be excluded. Patients whom have either midline shift, or any signs of herniation (even if disease has been treated with GK) will be excluded. Subjects with previously treated brain metastases may participate provided they are 1) stable (without clinical evidence of progression) 2) are out at least 10 days from CNS radiation and 3) and are not using steroids as part of treatment for their brain lesions for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

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

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

13) Has an active infection requiring systemic therapy.

14) 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.

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

16) 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.

17) Is HIV positive

18) Has evidence of active Hepatitis B virus or Hepatitis C virus.

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

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

20) Has significant cardiovascular disease including unstable angina pectoris, uncontrolled hypertension, uncontrolled arrhythmias, or severe valvular heart disease, or a myocardial infarction within 6 months prior to the first dose of study treatment.

21) Has an active bleeding disorders or evidence of chronic or acute disseminated intravascular coagulation (DIC).

22) Requires concomitant therapeutic anticoagulation (i.e., warfarin) for reasons other than venous catheter patency.

23) Has been classified according to the New York Heart Association classification as having Class III or IV heart disease (Section 11.4).

5.2 Trial Treatments

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

Table 2: Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Arms A and B: Days 1, 43, 64, and 85 Arm C: Days 22, 43, 64, and 85	IV infusion	Subjects who have measurable disease (based on RECIST 1.1) outside of the radiation field and who have derived benefit from the initial 4 doses of pembrolizumab may continue to receive pembrolizumab every 3 weeks for up to 2 years.	Experimental
Radiation Therapy	**Dose/ Potency**	**Dose Frequency**		**Regimen/ Treatment Period**	**Use**
HDCRT-lesions that have not been previously radiated	24 Gy in 3 fractions of 8Gy each for bone and/or soft tissue lesions 30 Gy in 5 fractions of 6 Gy each for prostate gland	3-5 days		The length of time for administration of the HDCRT will depend on the site of disease that is to be radiated. HDCRT will begin on day 1 for Arms A and C and will begin on day 22 for Arm B.	Part of clinical care as recommended for any tumor and/or metastatic site

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
HDCRT-previously radiated lesions	25 Gy in 5 fractions	5 days		HDCRT will begin on day 1 for Arms A and C and will begin on day 22 for Arm B.	Part of clinical care as recommended for any tumor and/or metastatic site

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

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

5.2.1.2 Preparation and Administration of Pembrolizumab

The commercial Pembrolizumab product provided by Merck will be prepared and administered per standard practice.

5.2.1.3 Administration of HDCRT

5.2.1.3.1 Overview

HDCRT will be administered to the primary tumor and/or sites of metastatic disease (1 or more sites permitted) over a period of 3-5 days. The length of time for administration of the HDCRT will depend on the site of disease that is to be radiated and whether a site of disease has been radiated previously.

Lesions that have not been previously radiated: HDCRT will begin on day 1 for Arms A and C and will begin on day 22 for Arm B. HDCRT will be administered at a constant dose for sites of tumor involvement: 24 Gy in 3 fractions of 8 Gy each for bone and/or soft tissue lesions; 30 Gy in 5 fractions of 6 Gy each for prostate gland.

Previously radiated lesions: HDCRT will begin on day 1 for Arms A and C and will begin on day 22 for Arm B. HDCRT will be administered at a constant dose for sites of tumor involvement: 25 Gy in 5 fractions of 5 Gy each for all previously radiated lesions, regardless of site of disease.

5.2.1.3.2 CT Simulation

CT simulation will be performed to permit customized treatment plans, and 3-D conformal or intensity-modulated radiation therapy plans are permitted. Patients who receive prostate

gland treatment will be immobilized in a vacuum-lock bag, and other sites of treatment will require immobilization at the discretion of the treating physician. Planning CT scans will be obtained with maximum 3mm slice thickness.

Radiation Treatment Planning

Computerized treatment planning is required for treatment on this protocol, and 3-D conformal or IMRT planning is permitted. Photon energies in the range of 6-15 MV are permitted. Arc-based therapy and Tomotherapy are permitted.

Planning Target Volume (PTV)

The clinical target volume (CTV) will consist of the gross tumor volume, including gross tumor volume with any extensions. The PTV_{tumor} will consist of a 2-7 mm expansion from the CTV_{tumor} to account for organ motion and set up error. A margin of 3-10 mm may be added to CTV_{tumor} to create the PTV_{tumor}.

The isodose line used for the prescription dose must cover a minimum of 95% of the PTV.

5.2.1.3.3 Image-Guidance

Daily confirmation of target volume position is required. Daily kV-kV matching, cone beam CT, or megavoltage CT will be performed prior to all treatments.

5.2.1.4 Dose Modification

5.2.1.4.1 Dose Modification of Pembrolizumab (Escalation/Titration/Other)

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.6 for supportive care guidelines, including use of corticosteroids.

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

General instructions:

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

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	

Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyper-thyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

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

NOTE:

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

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

5.2.1.4.2 Dose Modifications of HDCRT

There will be no dose modifications of HDCRT.

5.2.2 Timing of Dose Administration

Trial treatment should be administered after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0).

All trial treatments will be administered on an outpatient basis.

A schedule for return visits should be established at the first visit. If a participant misses a treatment, the missed treatment will be administered as soon as possible, so that subsequent treatments will be given in the appropriate intervals. Treatment may be continued for an additional time period, if needed. Participants who are treated outside of the established schedule should return to the original schedule as soon as possible.

Table 4: Delayed Visits for Reasons Other Than Toxicity

Treatment Period*	Range of Days	Protocol Deviation
HDCRT (administered over 3-5 consecutive business days)	± 3 days	No
	± 4 or more days	Yes
Pembrolizumab	± 3 days	No
	± 4 or more days	Yes
Biopsy/Research Bloods	± 3 days	No
	± 4 or more days	Yes
Clinical Labs (beginning after Day 1)	± 3 days	No
	± 4 or more days	Yes
Scans	± 14 days	No
	± 15 or more days	Yes

Follow-up	± 14 days	No
30-days after last dose of pembrolizumab	± 15 or more days	Yes
Follow-up		
After early discontinuation for reasons other than disease progression	± 28 days	No
Every 12 weeks for up to 2 years.	±29 days	Yes

*A participant will be taken off protocol treatment if more than one study drug administration or procedure is delayed contributing to a protocol deviation during the treatment period.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion. Every effort will be made 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 commercial Pembrolizumab product provided by Merck will be prepared and administered per standard practice.

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 Randomization or Treatment Allocation

Randomization will be discussed with participants during the process of informed consent and will occur after registration and within 10 days prior to the start of treatment. The randomization codes are generated by the study statisticians and stored in the Cancer Center Clinical Trials Database. Subjects should receive their first study treatment within 2 weeks of registration.

5.4 Stratification

Subjects will be stratified by mutation frequency status (high or low) based upon figure 1 results in Alexandrov *et al.* (17). High status will include all cancers types listed from kidney papillary and above. Low status will include all cancer types listed below kidney papillary and any additional type not included in the figure.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy may

be required. The investigator should discuss any questions regarding this with the Sponsor-Investigator. The final decision on any supportive therapy or vaccination rests with the Sponsor-Investigator and/or the subject's primary physician.

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. Participants will be maintained on drugs that they were taking prior to study entry unless a change in regimen is medically indicated.

Examples of Permitted medications or treatments

- Anti-androgen therapy
- Hormonal therapies
- Nonsteroidal anti-inflammatory agents
- Anti-histamines (e.g. Claritin®, Allegra®)
- Topical corticosteroids are acceptable, including steroids with very low solubility administered nasally for local effects only (e.g. Nasonex®).
- Short-term therapy for acute conditions not specifically related to tumor (except those listed under Section 5.5.2)
- Chronic medications (except those listed in Section 5.5.2)

All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

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

5.5.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy not specified in this protocol
    - Note: Stereotactic radiation therapy to up to 3 brain metastases may be allowed at the investigator's discretion.

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

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

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

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines for Pembrolizumab

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

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

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

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.

- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

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

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

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

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

- **Hypophysitis**:

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

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

- **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
  - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
- **Grade 3-4** hyperthyroidism
  - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

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

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

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

  Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 5: Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds	**Stop Infusion and monitor symptoms.** Additional appropriate medical	Subject may be premedicated 1.5h (± 30 minutes) prior to

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
<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	**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	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
indicated	investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence† from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

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 subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Use in Pregnancy

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

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and followed as described above and in Section 7.2.8.

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

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

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

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

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved (Section 5.8.1)
- Unacceptable adverse experiences as described in Section 5.2.1.4
- 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
- Initiation of alternate anti-cancer therapies.
- Initiation of non-permitted medications.
- Treatment delays as specified in Section 5.2.2.
- Administrative reasons
- Completed 24 months of uninterrupted treatment with pembrolizumab or 34 administrations of study medication, whichever is later.

  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.4.

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 7.1.5.3.1). Reason for subject withdrawal/discontinuation will be recorded in the cancer center database. Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status as specified in Section 6. Survival follow-up may be completed by telephone. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8.1 Treatment after Initial Radiologic Progression

If radiologic imaging shows progressive disease (PD), tumor assessment may be repeated ≥4 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued as per treatment calendar. If repeat imaging confirms progressive disease, subjects will be discontinued from study therapy. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions, with the exception of radiated lesions, which will only be considered when evaluating increased tumor burden. The decision to continue study treatment after the first evidence of disease progression is at the Investigator's discretion and will be based on the clinical status of the subject. Subjects may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression)

requiring urgent alternative medical intervention

Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation.

5.8.2 Discontinuation of Study Therapy after CR (applicable for subjects with disease outside of the radiation field)

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.5.4.

5.9 Subject Replacement Strategy

5.9.1 Replacement of Study Participants

A participant who is enrolled but who does not receive study drug or any of the study related procedures may be replaced. Every attempt will be made to evaluate any data from these participants for endpoint assessment.

5.10 Clinical Criteria for Early Trial Termination

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

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

2. Poor adherence to protocol and regulatory requirements

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

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

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

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart- Initial treatment Phase

Studies & Tests			Active Treatment																		
Arm A: Cycle			**1**														**2**			**3**	**4**
Scheduling Window (Refer to Table 4)																					
	Day	**Pre**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**23**	**24**	**25**	**26**	**29**	**36**	**43**	**50**	**57**	**64**	**85**
Informed Consent		X[a]																			
Inclusion/Exclusion Criteria		X[b]																			
Pathology review		X[a]																			
Demographics and Medical History		X[b]																			
Disease History		X[b]																			
Physical Exam/Vitals[e]		X[b]	X							X							X			X	X
Prior and concomitant medication		X[b]	X							X							X			X	X
AE assessment		X[b]	X							X							X			X	X
Height		X[a]																			
Weight		X[b]	X							X							X			X	X
ECOG PS		X[b]	X							X							X			X	X
HIV/HBV/HCV screening		X[c]																			
Pregnancy test-urine or serum		X[d]	X[f]																		
CBC with diff		X[b]	X[m]					X	X	X					X	X	X	X	X	X	X
Comprehensive chem. panel[v]		X[b]	X[m]					X	X	X					X	X	X	X	X	X	X
Serum biomarkers[k]		X[b]								X							X			X	X
LDH		X[b]								X							X			X	X
PT/PTT and INR		X[b]								X[u]							X[u]				
T3, FT4 and TSH			X														X				X
Urinalysis			X														X				
Biopsy			X[h]							X							X				
Research bloods for immunologic testing			X							X							X			X	X
HDCRT			X	X	X	X[r]	X[r]														
Pembrolizumab			X														X			X	X
Tumor imaging		X[l]																			X[i]
Symptom Diary			X							X							X			X	X

Studies & Tests			Active Treatment																	
Arm B: Cycle			**1**													**2**			**3**	**4**
Scheduling Window (Refer to Table 4)																				
	Day	**Pre**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**23**	**24**	**25**	**26**	**29**	**36**	**43**	**50**	**57**	**64**	**85**
Informed Consent		X[a]																		
Inclusion/Exclusion Criteria		X[b]																		
Pathology review		X[a]																		
Demographics and Medical History		X[b]																		
Disease History		X[b]																		
Physical Exam/Vitals[e]		X[b]	X							X							X			X	X
Prior and concomitant medication		X[b]	X							X							X			X	X
AE assessment		X[b]	X							X							X			X	X
Height		X[a]																			
Weight		X[b]	X							X							X			X	X
ECOG PS		X[b]	X							X							X			X	X
HIV/HBV/HCV screening		X[c]																			
Pregnancy test-urine or serum		X[d]	X[f]																		
CBC with diff		X[b]	X[m]					X	X	X					X	X	X	X	X	X	X
Comprehensive chem. Panel[v]		X[b]	X[m]					X	X	X					X	X	X	X	X	X	X
Serum biomarkers[k]		X[b]								X							X			X	X
LDH		X[b]								X							X			X	X
PT/PTT and INR		X[b]								X[u]							X[u]				
T3, FT4 and TSH			X														X				X
Urinalysis			X														X				
Biopsy			X[h]							X							X				
Research bloods for immunologic testing			X							X							X			X	X
HDCRT										X	X	X	X[r]	X[r]							
Pembrolizumab			X														X			X	X
Tumor imaging		X[l]																			X[i]
Symptom Diary			X							X							X			X	X

Studies & Tests			Active Treatment																		
Arm C: Cycle										**1**							**2**			**3**	**4**
Scheduling Window (Refer to Table 4)																					
	Day	**Pre**	**1**	**2**	**3**	**4**	**5**	**8**	**15**	**22**	**23**	**24**	**25**	**26**	**29**	**36**	**43**	**50**	**57**	**64**	**85**
Informed Consent		X[a]																			
Inclusion/Exclusion Criteria		X[b]																			
Pathology review		X[a]																			
Demographics and Medical History		X[b]																			
Disease History		X[b]																			
Physical Exam/Vitals[e]		X[b]	X						X	X							X			X	X
Prior and concomitant medication		X[b]	X						X	X							X			X	X
AE assessment		X[b]	X						X	X							X			X	X
Height		X[a]																			
Weight		X[b]	X						X	X							X			X	X
ECOG PS		X[b]	X						X	X							X			X	X
HIV/HBV/HCV screening		X[c]																			
Pregnancy test-urine or serum		X[d]								X[g]											
CBC with diff		X[b]	X[m]							X					X	X	X	X	X	X	X
Comprehensive chem. Panel[v]		X[b]	X[m]							X					X	X	X	X	X	X	X
Serum biomarkers[k]		X[b]								X							X			X	X
LDH		X[b]								X							X			X	X
PT/PTT and INR		X[b]								X[u]							X[u]				
T3, FT4 and TSH			X														X				X
Urinalysis										X							X				
Biopsy			X[h]							X							X				
Research bloods for immunologic testing			X							X							X			X	X
HDCRT			X	X	X	X[r]	X[r]														
Pembrolizumab										X							X			X	X
Tumor imaging		X[l]																			X[i]
Symptom Diary			X						X	X							X			X	X

	Active Treatment for subjects who have disease outside of the radiation field		**End of Treatment**	**Post-treatment**		
Treatment Cycle (All Arms)	**To be repeated beyond 6 cycles. Beginning with cycle 5, each cycle is 3 weeks.**					
	Cycle 5	**Cycle 6**	**Discontinuation of pembrolizumab[j]**	**Safety follow-up Discontinuation of pembrolizumab**	**Follow-up visits[n]**	**Survival follow-up[o]**
Scheduling Window (Refer to Table 4)						
			At the time of discontinuation of pembrolizumab	30 days post-discontinuation	Every 12 weeks post discontinuation up to 2 years from study entry or per footnote	Annually
Physical Exam/Vitals[e]	X	X	X	X		
AE assessment	X	X	X	X	X[s]	
Prior and concomitant medication review	X	X	X	X		
Weight	X	X				
ECOG PS	X	X	X	X		
CBC with diff	X	X	X	X		
Comprehensive chem. Panel[v]	X	X	X	X		
Serum biomarkers[k]	X	X	X	X	X	
LDH	X	X	X	X		
PT/PTT and INR	X[u]	X[u]	X[u]		X[u]	
T3, FT4 and TSH	X[w]		X	X		
Urinalysis	X[w]		X	X		

	Active Treatment for subjects who have disease outside of the radiation field		**End of Treatment**	**Post-treatment**		
Treatment Cycle (All Arms)	**To be repeated beyond 6 cycles. Beginning with cycle 5, each cycle is 3 weeks.**					
	Cycle 5	**Cycle 6**	**Discontinuation of pembrolizumab[j]**	**Safety follow-up Discontinuation of pembrolizumab**	**Follow-up visits[n]**	**Survival follow-up[o]**
Scheduling Window (Refer to Table 4)						
			At the time of discontinuation of pembrolizumab	30 days post-discontinuation	Every 12 weeks post discontinuation up to 2 years from study entry or per footnote	Annually
Biopsy for research[q]	X	X	X		X	
Research bloods for immunologic testing	X[t]	X[t]	X	X	X	
Pembrolizumab	X	X				
Tumor Imaging[p]	per standard clinical practice based on tumor site, or a minimum of every 12 weeks[i]		X		X	
Symptom Diary	X	X	X	X		
Post-study anticancer therapy status					X	X
Survival Status						X

[a] May be completed at any time prior to registration.
[b] Pre-study, within 10 days of registration.
[c] Pre-study, within 6 months of registration
[d] Pre-study, within 2 weeks of registration.
[e] A complete physical exam should be completed at screening. Symptom-directed physical exams may be conducted at all other visits.

[f] Must be completed within 72 hours prior to receiving the first dose of study drug. If the screening test is completed within 72 hours prior to Day 1, this test does not need to be repeated.
[g] Must be completed within 72 hours prior to receiving the first dose of study drug.
[h] Required only if a pre-study biopsy is not available or if a subject has received prior radiation at a tumor site and will be re-radiated at that tumor site as part of the proposed study. The pre-study biopsy may be obtained up to 6 weeks prior to initiation of treatment on Day 1. There should be no intervening treatment in between the pre-study biopsy and Day 1.
[i] Subjects with progressive disease should undergo a second scan at least 4 weeks later to confirm progression and exclude the possibility of tumor flare reaction, according to irRc guidelines.
[j] If a subject is discontinued and the assessments have been completed as part of a regularly scheduled visit, the assessments do not need to be repeated. Tumor imaging does not need to be repeated if scans have been completed within the past 8 weeks.
[k] Only when available.
[l] Tumor imaging should be completed within 28 days of registration.
[m] Not required if the screening laboratory analyses were completed within 7 days of Day 1.
[n] If a subject discontinues pembrolizumab without documented disease progression, every effort will be made to monitor their disease until (1) the start of new anti-cancer treatment, (2) disease progression, (3) death, (4) withdraw of consent or lost to follow-up, (5) the end of the follow-up visit period, or (6) the end of the study, whichever occurs first.
[o] Survival follow-up may be completed by phone.
[p] Tumor imaging will be completed per standard clinical practice for each disease, or a minimum of every 12 weeks. Tumor imaging does not need to be repeated if scans have been completed within the past 4 weeks.
[q] Optional: If subjects develop metastatic deposits accessible to biopsy/excision with minimal morbidity, a specimen may be collected.
[r] Required for subjects receiving HDCRT to their prostate gland and for subjects receiving HDCRT to lesions that were radiated previously.
[s] All AEs occurring within 30 days after the last dose of trial treatment will be recorded. SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever comes first, will be recorded. Afterwards, only SAEs and ECIs that are related to trial treatment will be reported.
[t] Research bloods for immunologic testing should be collected at cycles 5, 10, 15, 20, 25, 30, 34.
[u] To be performed if an optional biopsy is scheduled for that day or if there were changes in PT/PTT and INR (Grade 2 or higher) at the prior time point. PT/PTT and INR should be completed prior to the biopsy.
[v] Refer to Table 6 for a complete list of labs that need to be completed.
[w] To be repeated every 2 cycles after Cycle 4.

6.2 Study Flow Chart- Second Course Phase

		Treatment cycles (3-Week Cycles)		End of Treatment	Post-treatment		
		To be repeated beyond cycle 3					
Treatment Cycle/Title	1	Cycle 2	Cycle 3	Discontinuation of pembrolizumab[h]	Safety follow-up Discontinuation of pembrolizumab	Follow-up visits [i]	Survival follow-up [j]
Scheduling Window (Refer to Table 4)							
				At the time of discontinuation of pembrolizumab	30 days post-discontinuation	Every 12 weeks post discontinuation up to 2 years from initiating second-course treatment or per footnote	Annually
Eligibility Criteria	X[a]						
Physical Exam/vitals[b]	X	X	X	X	X		
AE assessment	X	X	X	X	X	X[k]	
Prior and concomitant medication review	X	X	X	X	X	X	
Weight	X	X	X				
ECOG PS	X	X	X	X	X		
Pregnancy test-urine or serum β-HCG	X[m]						
CBC with diff	X	X	X	X	X		
Comprehensive chem. panel[l]	X	X	X	X	X		
Serum biomarkers[c]	X	X	X	X	X	X	
LDH	X	X	X	X	X		
PT/PTT and INR	X[d]	X[d]	X[d]	X[d]		X	
T3, FT4 and TSH			X[n]	X	X		
Urinalysis	X		X[n]	X	X		
Biopsy[e]	X	X	X	X		X	

		Treatment cycles (3-Week Cycles)		End of Treatment	Post-treatment		
		To be repeated beyond cycle 3					
Treatment Cycle/Title	**1**	**Cycle 2**	**Cycle 3**	**Discontinuation of pembrolizumab[h]**	**Safety follow-up Discontinuation of pembrolizumab**	**Follow-up visits [i]**	**Survival follow-up [j]**
Scheduling Window (Refer to Table 4)							
Research bloods for immunologic testing	X			X	X	X	
Pembrolizumab	X	X	X	X			
Tumor imaging		per standard clinical practice based on tumor site, or a minimum of every 12 weeks[f]		X[g]		X[g]	
Symptom Diary	X	X	X	X	X		
Post-study anticancer therapy status						X	X
Survival Status							X

[a] Subjects who either a) attain a CR and discontinue treatment or b) discontinue treatment after 24 months on pembrolizumab for reasons other than disease progression or intoloerability may restart trial treatment if they meet the criteria specified in Section 7.1.5.4.
[b] A complete physical exam should be completed at cycle 1. Symptom-directed physical exams may be conducted at all other visits.
[c] Only when available
[d] To be performed if there is an optional biopsy scheduled for that day or if there were changes in PT/PTT and INR (Grade 2 or higher) at the prior time point. PT/PTT and INR should be completed prior to the biopsy.
[e] Optional: If subjects develop metastatic deposits accessible to biopsy/excision with minimal morbidity, a specimen may be collected.
[f] Subjects with progressive disease should undergo a second scan at least 4 weeks later to confirm progression and exclude the possibility of tumor flare reaction, according to irRc guidelines.
[g] Tumor imaging will be completed per standard clinical practice for each disease. Tumor imaging does not need to be repeated if scans have been completed within the past 4 weeks.
[h] If a subject is discontinued and the assessments have been completed as part of a regularly scheduled visit, the assessments do not need to be repeated. Tumor imaging does not need to be repeated if scans have been completed within the past 8 weeks.
[i] If a subject discontinues pembrolizumab without documented disease progression, every effort will be made to monitor their disease

until (1) the start of new anti-cancer treatment, (2) disease progression, (3) death, (4) withdraw of consent or lost to follow-up, (5) the end of the follow-up visit period, or (6) the end of the study, whichever occurs first.

[j] Survival follow-up may be completed by phone.

[k] All AEs occurring within 30 days after the last dose of trial treatment will be recorded. SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever comes first, will be recorded. Afterwards, only SAEs and ECIs that are related to trial treatment will be reported.

[l] Refer to Table 6 for a complete list of labs that need to be completed.

[m] Must be completed within 72 hours prior to receiving the first dose of study drug.

[n] To be repeated every 2 cycles after Cycle 2.

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-Investigator 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.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Registration

All participants must sign the consent form prior to determination of eligibility for this study. All participants who meet the inclusion/exclusion criteria may be registered. Registration will occur following verification of eligibility by the treating physician. Participants should receive their first study treatment within 2 weeks of registration.

7.1.1.4 Medical History

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

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

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

7.1.1.5.2 Concomitant Medications

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

7.1.1.6 Disease Details and Treatments

7.1.1.6.1 Disease Details

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

7.1.1.6.2 Prior Treatment Details

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

7.1.1.6.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit should 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.

7.1.1.7 Assignment of Randomization Number

The randomization codes are generated by the study statisticians and stored in the UVA Cancer Center Clinical Trials Database.

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

Treatment compliance may be evaluated through drug accountability assessments and through the evaluation of subject medical records and CRF documents.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

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

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

7.1.2.2 Full Physical Exam

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

7.1.2.3 Directed Physical Exam

For time-points 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.

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs 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.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 11.1) as specified in the Trial Flow Chart (Section 6.0).

7.1.2.6 Tumor Imaging and Assessment of Disease

7.1.2.6.1 Serum Markers of Disease Activity.

Serum markers of disease activity will be collected at the Investigators discretion per standard clinical practice,

7.1.2.6.2 Tumor Imaging

Tumor imaging may include CT/PET-CT scans or MRI, but the same method of assessment will be used to evaluate tumor burden at baseline and throughout the course of the study.

Imaging should include the chest, abdomen, and pelvis at all timepoints specified. Additional imaging (e.g. brain, neck) is not required, but will be completed per clinical practice or if metastases to these sites are clinically suspected. Bone scans will be completed per clinical practice for those patients with bone metastases or for patients where these scans are clinically indicated.

7.1.2.6.3 Tumor Measurements

For subjects who have disease both inside and outside of the radiation field, RECIST 1.1 Criteria will be used to evaluate clinical response (18,19). In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions with the exception of radiated lesions, which will only be considered when evaluating for increased in tumor burden. Partial or complete responses will be confirmed by a repeat radiographic assessment ≥ 4 weeks from the time that the response was initially documented. If radiologic imaging shows PD, tumor assessment may be repeated ≥4 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression (Section 5.8.1). If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued as per treatment calendar.

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

7.1.2.7.1 Core Biopsies

Core biopsies (4) will be taken of at least one HDCRT-treated lesion. A maximum of (4) biopsies of unirradiated lesions may also be collected, when tissue is available. The tissue specimens will be collected in the following

- (1) Formalin-fixed for paraffin embedding (TMA for IHC and TCR sequencing; ideally the sample should be large enough to be able to cut 8-10 slides)
- (2) RPMI for single cell suspensions (flow cytometric analyses)

- (1) Trizol for RNA extraction (gene expression analyses)

Leftover samples may be banked and stored for future biomedical research.

On the days when both study intervention and biopsies are scheduled, biopsies should be completed prior to the study intervention.

7.1.2.7.2 Blood Collection for Research Analyses

The following blood samples for research will be collected and processed by the UVA Biorepository and Tissue Research Facility (BTRF).

- 80 cc blood collected in heparinized green top tubes for lymphocytes.

Research bloods will be collected as specified in the Trial Flow Chart (Section 6.0).

Leftover samples may be banked and stored for future biomedical research.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below in Table 6.

Table 6: Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum biomarkers (when available)
Hemoglobin	Alkaline phosphatase	Glucose	HIV testing [2]
Platelet count	Alanine aminotransferase (ALT)	Protein	PT/PTT
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	INR
Red Blood Cell Count	Carbon Dioxide	Microscopic exam *(If abnormal)*	Total triiodothyronine (T3)
Absolute Neutrophil Count	*(CO_2 or biocarbonate)*	results are noted	Free thyroxine (T4)
Absolute Lymphocyte Count	Uric Acid	Urine pregnancy test [1]	Thyroid stimulating hormone (TSH)
	Calcium		HBV testing[3]
	Chloride		HCV testing[3]
	Glucose		Blood for correlative studies
	Phosphorus		Serum β-human chorionic gonadotropin†
	Potassium		(β-hCG)†
	Sodium		Lactate dehydrogenase (LDH)
	Magnesium		Direct Bilirubin *(May be completed at the time of the chemistry during MK3475 treatment days, or if total bilirubin is elevated above the upper limit of normal)*
	Total Bilirubin		
	Total protein		
	Blood Urea Nitrogen		

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

[2] HIV screening (antibody screen); if the antibody screen is positive, follow-up testing by RNA analysis may be completed to determine whether active disease is present.

[3] HBV and HCV screening (antibody screen); if the antibody screen is positive, follow-up testing by RNA analysis may be completed to determine whether active disease is present.

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 or study intervention.

7.1.4 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2.

7.1.5 Visit Requirements

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

7.1.5.1 Screening

A member of the study team will explain the purpose of the study and the study-related procedures to potential subjects. Subjects will be asked to provide written informed consent prior to the initiation of any study-related procedures. The results from assessments performed as part of a subject's clinical care prior to receipt of informed consent may be utilized to fulfill a screening requirement, if the assessments were completed with the required window for screening.

7.1.5.2 Treatment Period

The treatment period will begin on Day 1 and will continue until the subject completes the treatment regimen or discontinues/withdraws from treatment (please refer to Section 5.8).

7.1.5.2.1 End of Treatment Visit

This visit will occur at the time that a subject is discontinued from the study.

7.1.5.3 Post-Treatment Visits

7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All Aes that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or baseline, 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.

7.1.5.3.2 Follow-up Visits

- Subjects who discontinue for reasons other than progressive disease will move into post-treatment follow-up until disease progression, initiating a non-study cancer treatment, death, or withdrawing consent or becoming lost to follow-up. Follow-up visits will occur every 12 weeks post discontinuation up to 2 years from study entry or until resolution of toxicity (whichever is longer). Subjects will then be followed annually for survival.

- After documented disease progression each subject will be followed annually (may be completed by telephone) for overall survival, until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.5.3.3 Survival Follow-up

Subjects who complete 2 years of therapy or who complete the follow-up phase will move into survival follow-up.

Subjects who experience confirmed disease progression or who start a new anti-cancer therapy, will also move into survival follow-up and should be contacted by telephone annually to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.5.4 Second Course Phase (Retreatment Period)

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

- **Either**

  - Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1, and

    - Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy

    - Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

    OR

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

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab, and
- Meets the safety parameters listed in the inclusion/exclusion criteria

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

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

7.2 Assessing, Recording, and Reporting Adverse Events

7.2.1 Time Span for Recording Adverse Events

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.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded 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 7.2.8. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

7.2.2 Definitions

Adverse event (AE): 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 study drug or protocol-specified procedure, 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.

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, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Unexpected AE – Any adverse event not listed in Section 7.2.6.

Serious AE: A serious adverse event is any adverse event occurring at any dose during the study 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 another important medical event

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;

Unanticipated problem – An unanticipated problem is any event/experience that meets ALL 3 criteria below:

- Is unexpected in terms of nature, severity or frequency given the research procedures that are described in the protocol-related documents AND in the characteristics of the participant population being studied.

- Is related or possibly related to participation in research. This means that there is a reasonable possibility that the incident may have been caused by the procedures involved in the research study.

- The incident suggests that the research placed the participant or others at greater risk of harm than was previously known or recognized OR results in actual harm to the participant or others.

Protocol Violation- A protocol violation is defined as any change, deviation, or departure from the study design or procedures of a research project that is NOT approved by the institution's IRB prior to its initiation or implementation, OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations. Protocol violations may or may not be under the control of the study team or Uva staff. These protocol violations may be major or minor violations.

Suspected Adverse Reaction (as defined in 21 CFR 312.32 (a))- Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.

7.2.3 Attribution Assessment

Attribution – The determination of whether an adverse event is related to a medical treatment or procedure. Please refer to Table 7 for additional guidance on evaluation of attribution.

Definite – Applies to those adverse events which, the investigator feels are incontrovertibly related to study drug. An adverse event may be assigned an attribution of definitely related if or when (must have all of the following):

- It follows a reasonable temporal sequence from administration of the test drug.
- It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
- It disappears or decreases on cessation or reduction in dose with re-exposure to drug. (Note: This is not to be constructed as requiring re-exposure of the subject; however, the group of definitely related can only be used when a recurrence is observed.)
- It follows a known pattern of response to the test drug.

Probable – Applies to those adverse events for which, after careful consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the test drug. An adverse event may be considered probably related if or when (must have three of the following):

- It follows a reasonable temporal sequence from administration of the test drug.
- It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
- It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists (e.g. bone marrow depression, fixed drug eruptions, tardive

dyskinesia).
- It follows a known pattern of response to the test drug.

Possible – Applies to those adverse events for which, after careful consideration at the time they are evaluated, a connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An adverse event may be considered possibly related if or when (must have two of the following):

- It follows a reasonable temporal sequence from administration of the test drug.
- It could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
- It follows a known pattern of response to the test drug.

Unlikely – Applies to those adverse events for which, after careful consideration at the time they are evaluated, are judged to be unrelated to the test drug. An adverse event may be considered unlikely if or when (must have two of the following):

- It does not follow a reasonable temporal sequence from administration of the test drug.
- It could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
- It does not follow a known pattern of response to the test drug.
- It does not reappear or worsen when the drug is re-administered.

Unrelated – Applies to those adverse events, which after careful consideration, are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).

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 7: 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 for an elective procedure to treat a preexisting condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); 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) (although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. 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 to the Sponsor and to Merck within 2 working days.	
	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 Merck product to be discontinued?	
Relationship to test drug	Did Merck product cause the adverse event? The determination of the likelihood that 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 Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to 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 Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was 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 theSponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to 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) Sponsor's 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 MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding 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 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 Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.
No, there is not a reasonable possibility of Merck product relationship		Subject did not receive Merck product OR temporal sequence of the AE onset relative to administration of Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a subject with overdose without an associated AE.)

7.2.5 Adverse Event Classifications

Adverse events (Aes) are classified into sections, specified in the CTCAE v4.03. For specific classifications pertaining to the protocol, we specify the following:

Hematologic/Metabolic- Any AE coded under one of the following CTCAE v4.03 categories should be reported under the Hematologic/Metabolic adverse event classification:

Table 8: Hematologic/Metabolic Classifications

Section	AE
Blood and lymphatic	Anemia Leukocytosis
Investigations	**ALL EXCEPT:** Carbon monoxide diffusing capacity decreased Ejection fraction decreased Forced expiratory volume decreased Vital capacity abnormal Weight gain Weight loss
Metabolism and nutrition disorders	**ALL EXCEPT:** Alcohol intolerance Anorexia Dehydration Glucose intolerance Iron overload Obesity Tumor lysis syndrome

Non-hematologic/Non-Metabolic- Any AE not reported under hematologic/metabolic, ocular, or allergic/autoimmune, should be reported under the non-hematologic/non-metabolic adverse event classification.

Ocular – Any AE coded under one of the following CTCAE v4.03 Adverse Event Terms should be reported under the Ocular adverse event classification:

- Eye Disorders: Night blindness (nyctalopia)
- Eye Disorders: Papilledema
- Eye Disorders: Retinopathy

- Eye Disorders: Blurred vision
- Eye Disorders: Flashing lights
- Eye Disorders: Floaters

Allergic/Autoimmune – Only Aes coded as Immune System Disorder: Allergic reaction, autoimmune disorder, or anaphylaxis should be reported under the

Allergic/Autoimmune adverse event classification. Other Aes coded under Immune System Disorder should be reported under Non-hematologic/Non-metabolic.

7.2.6 Agent-Specific Expected Adverse Events List

7.2.6.1 Pembrolizumab

Treatment-related adverse reactions are described in Section 7 of the Investigator's Brochure.

7.2.6.2 Adverse Events Considered Expected for HDCRT

Expected toxicities related to HDCRT (highest grade expected—Grade 2)

- Esophagitis
- Pneumonitis
- Fatigue
- Dermatitis (erythema, edema, low risk of desquamation)
- Urinary frequency, dysuria, urgency, nocturia
- Diarrhea, tenesmus
- Hematochezia
- Gross hematuria
- Urethral stricture
- Bone fracture
- Temporary need for urinary catheter

Expected toxicities related to HDCRT (highest grade expected—Grade 3)

- Erectile dysfunction

7.2.6.3 Adverse events expected from biopsies

Adverse events expected from biopsies (highest grade expected—Grade 2)

- Bleeding
- Bruising
- Pain
- Lymphedema
- Delayed wound healing
- Scarring
- Numbness
- Gross hematuria and/or dysuria and urinary frequency (prostate biopsies)
- hematochezia (prostate biopsies)
- Infection

7.2.7 Dose Limiting Toxicities

A DLT of pembrolizumab is defined as an unacceptable, drug-related toxicity requiring permanent discontinuation, per Table 3 (Dose Modification Guidelines for Drug-Related Adverse Events).

7.2.8 Recording and Reporting Adverse Events

7.2.8.1 Process for Recording Adverse Events

Dose-limiting toxicities (DLTs)

DLTs will be entered into Oncore within 5 calendar days of the study team learning of the event. DLTs that are deemed serious and unexpected will be submitted to the IRB per institutional guidelines (see below).

Other Aes

Aes must be recorded into the University of Virginia Cancer Center OnCore database per the following guidelines:

Table 9: Recording Aes into the OnCore Database

High Risk Studies Reporting requirements for Aes that occur within 30 days of the last dose of protocol specified treatment								
	Grade 1	Grade 2		Grade 3				Grade 4 & 5
	Expected and unexpected	Expected	Unexpected	Expected		Unexpected		Expected and Unexpected
				Without hospitalization	With hospitalization	Without hospitalization	With hospitalization	
Unrelated Unlikely	OnCore 30 days[a]	OnCore 30 days	OnCore 30 days	OnCore 30 days	OnCore 15 days	OnCore 30 days	OnCore 15 days	OnCore 7 days
Possible Probable Definite	OnCore 30 days[a]	OnCore 30 days	OnCore 15 days	OnCore 30 days	OnCore 15 days	OnCore 7 days	OnCore 7 days	OnCore (24-hrs)* 7 days

*Enter into OnCore database within 24 hours if unexpected and definitely related to protocol specified treatment
Hospitalization defined as an inpatient hospital stay or prolongation of a hospital stay equal to or greater than 24 hours
[a] Grade 1 unexpected or expected hematologic/metabolic events will be recorded in the Cancer Center Database; however, regardless of attribution, these events do not have to be reported.

7.2.8.2 Recording Laboratory Values

Laboratory values specified in Table 6 will be recorded in the UVA Cancer Center database, graded using the CTCAE v4.03 (if a grading category exists) and reported as described in Section 7.2.7. Any abnormal laboratory values captured which are not included in the above list, but are considered to be pertinent positive clinical signs/symptoms will be recorded in the UVA Cancer Center database and reported as described in Section 7.2.7. If there is any doubt on the part of study personnel concerning what constitutes a pertinent positive finding, the Sponsor-Investigator will be consulted.

7.2.8.3 UVA IRB Reporting Requirements

The University of Virginia is responsible for reporting to the UVA IRB-HSR per the following guidelines:

Table 10: UVA IRB-HSR Reporting

Type of Event	To whom will it be reported:	Time Frame for Reporting	How reported?
Any internal event resulting in death that is deemed DEFINITELY related to (caused by) study participation (Note: An internal event is one that occurs in a subject enrolled in a Uva protocol.)	IRB-HSR	Within 24 hours	IRB Online and phone call www.irb.virginia.edu/
Internal, Serious, Unexpected adverse event.	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event. *Timeline includes submission of signed hardcopy of AE form.*	IRB Online www.irb.virginia.edu/
Unanticipated Problems that are not adverse events or protocol violations This would include a Data Breach.	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. *http://www.virginia.edu/vprgs/irb/HSR_docs/Forms/Reporting_Requirements-Unanticipated_Problems.doc*
Protocol Violations (*The IRB-HSR only requires that MAJOR violation be reported, unless otherwise required by your sponsor, if applicable.)* Or Enrollment Exceptions	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Violation and Enrollment Exception Reporting Form *http://www.virginia.edu/vprgs/irb/hsr_forms.html*

Data Breach	The Uva Corporate Compliance and Privacy Office and ITC: if breach involves electronic data- Uva Police if breach includes such things as stolen computers.	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified. IMMEDIATELY.	Uva Corporate Compliance and Privacy Office- Phone 924-9741 ITC: Information Security Incident Reporting procedure, http://www.itc.virginia.edu/security/reporting.html Phone- (434) 924-7166

7.2.8.4 Reporting to the FDA

The Sponsor-Investigator for the study (the UVA PI or designee) is responsible for providing safety updates to the FDA per the following guidelines. The reporting times refer to the time the study team received knowledge of the event.

FDA Reporting Requirements

- Serious and unexpected suspected adverse reactions will be reported to the FDA no later than 15 calendar days after the sponsor determines that the requirements for an IND safety report have been met. The FDA will be notified using an FDA Form 3500a.
- Unexpected fatal or life-threatening suspected adverse reactions will be reported to the FDA no later than 7 calendar days after the Sponsor receives the initial information of the event. The FDA will be notified using an FDA Form 3500a.
- Other adverse event information will be sent to the FDA in the IND annual report.

7.2.8.5 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) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be

reported by the investigator. All reported pregnancies 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).

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

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

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

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

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

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

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

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or the 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

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 following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor-Investigator and to Merck Global Safety.

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

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

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

7.2.8.8 Reporting Events of Clinical Interest

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

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

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

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.2.8.6, 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).

7.2.9 Sponsor-Investigator Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL ANALYSIS PLAN

8.1 Design

This is a pilot study of HDCRT and immunotherapy, and is proposed as a 3 arm randomized repeated measures design where all participants receive the same amount of treatment. Each participant will receive HDCRT and up to 34 doses of pembrolizumab, and it is the timing of HDCRT and pembrolizumab delivery that differs between the arms. Thus, the goal is to obtain preliminary data on the safety of HDCRT with immunotherapy, delivered concurrently (arm A) or sequentially (arms B and C) and to obtain preliminary estimates of change in T-cell frequency and activation among arms. The central hypothesis is that focused energy deposition HDCRT-induced immunogenic cell death will overcome limitations in antigen availability, and effective T-cell responses, and thereby enhance immune-therapy of advanced solid tumors. Our secondary hypothesis is that concomitant immune-activation will further augment $CD8^+$ T-cell responses to tumor antigen released by HDCRT. We will obtain preliminary data on whether HDCRT promotes the presence of $CD8^+$ T-cells in irradiated tumors, blood and non-irradiated tumor lesions.

Safety stopping rules will be employed within each arm and will be judged by DLTs as defined in Section 7.2.7. Endpoints include assessment of $CD8^+$ T-cells and $CD4^+Foxp3^+$ T-cells infiltration in solid tumors measured at baseline, day 21 and day 43. Secondary endpoints include additional measurements in the blood (day 1, 22, 43, 64 and 85), in non-irradiated tumors as feasible, and assessment of disease control. Safety will be assessed by the presence or absence of dosing limiting toxicities defined in Section 7.2.7.

Subjects will be stratified by mutation frequency status (high or low) as defined in Section 5.4. Within each stratum, subjects will be randomized based upon equal allocation among the arms until a safety bound has been triggered or target accrual has been met.

8.2 Sample Size

Target sample size is 6 evaluable participants per arm, which was chosen as a feasible number that could be accrued within a 2 year accrual period. The purpose is not to make definitive comparisons between arms but to obtain preliminary estimates of change in $CD8^+$ T-cells and $CD4^+Foxp3^+$ T-cells over time for the different treatment schedules. Participants are considered evaluable if they satisfy all inclusion and exclusion criteria and have adequate endpoint measurements from day 1 and day 22 tumor samples. Adjusting for a 15% unevaluable/drop-out rate maximum target accrual is estimated at 21 participants.

The main emphasis of this study is to obtain estimates of potential differences between arms, as well as within an arm over time; as such, with only 6 evaluable participants per arm, there is low power to make comparisons between arms. However, within an arm there is limited power to detect changes between day 1 and day 22 for $CD8^+$ T-cells. Data from Valdman et. Al. reported a mean (standard deviation) cell count per tissue microarray from 36 patients of 52.1 (36) and 10.2 (11) from malignant prostate tissue for $CD8^+$ T-cells and $Foxp3^+$ T-cells, respectively (20). Assuming these data are representative of our patient population, we have approximately 80% power to detect a doubling mean increase in $CD8^+$ T-cells (i.e., from 52 at day 1 to 104 at day 22).This level of change corresponds to an effect size of 1.44. Thus, for this study we will only be able to detect large changes in pre to post measures within each arm. Given the variability reported for $Foxp3^+$ T-cells (sd dev > mean) the power to detect a complete depletion of $Foxp3^+$ T-cells is limited. It is hoped that a consistent increasing or decreasing pattern will be observed in this pilot study.

8.3 Safety

Adverse Event Stopping Guidelines

The study will be monitored continuously for treatment-related adverse events.

DLTs defined in Section 7.2.7 will guide decisions about accrual and safety monitoring. Minimum observation time for DLTs is day 42. Accrual will continue by random arm assignment unless both of the first 2 patients within an arm or 3 of the first 6 participants within an arm experience DLTs. If 3 or more participants in any arm experience DLTs, that specific arm will be deemed too toxic and closed to further accrual. This decision rule is based upon Wald's sequential probability ratio test assuming lower and upper proportions of DLTs of 10% and 30%, respectively, with type I and II error rates of 10%.

8.4 Analyses

Adverse events and DLTs will be summarized by frequency and magnitude for each arm and overall. Analysis of variance and repeated measure models will be used to estimate the assumed rate of reaccumulation/replenishment in $CD8^+$ T-cells post HDCRT and the assumed rate of depletion for $Foxp3^+$ T-cells post HDCRT (i.e., to estimate group differences and changes over time in immune assay parameters in tumor and in PBMC). We realize that only large consistent differences may be detected given the limited sample size and heterogeneity among disease types. The effects of each treatment will be assessed over time for each study Arm, enabling preliminary estimates of associations with clinical response and preliminary estimates of difference in each measure among the 3 study Arms. Data estimates of differences in counts between day 1 and day 22 provide a preliminary assessment of whether the inclusion of pembrolizumab increases $CD8^+$ T-cell when compared to HDCRT alone or in conjunction with HDCRT. Initial estimates of change over time in the blood (from day 1 to day 85) and in the tumor (day 1 to day 43) will provide estimates of whether order, concurrent or sequential delivery of treatment, has an impact on counts. Additional estimates over time to day 385 in PBMC will provide preliminary data on the effect of additional cycles of pembrolizumab. Exploratory associations/cross classifications between change in on $CD8^+$ T cell and T regulatory cell (T_{reg}) infiltration in tumors, and clinical outcomes of response, progression-free survival and overall survival will be summarized.

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 11.

Table 11: Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
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 Study Conduct and Ethical Considerations

This study will be conducted in accordance with the standards of Good Clinical Practice, all applicable federal, state, and local laws, and in accord with the ethical principles that originated in the Declaration of Helsinki. The Principal Investigator (PI) will ensure that staff are trained and carry out the study in accord with the protocol specifications. The PI will ensure that all study site personnel are aware that the study protocol and all data generated are confidential and should not be disclosed to third parties (with the exception of local and national regulatory bodies which require access for oversight purposes).

10.2 UVA Institutional Review Board for Health Sciences Research

The UVA Institutional Review Board for Health Sciences Research (UVA IRB-HSR) will approve all aspects of this study, including the clinical trial protocol, informed consent documents, and patient materials. Modifications to the protocol or consent form will be reviewed and approved by the UVA IRB-HSR prior to implementation, except when necessary to eliminate apparent immediate hazards to the study participants. The study will undergo continuing IRB review based on the level of risk as assessed by the IRB. This review will take place no less than annually. Reporting to the UVA IRB-HSR will occur as specified in Section 7.2.7.

10.3 Consent Forms and the Consenting Process

Consent forms will be written in accord with 21 CFR 50 and will be reviewed and approved by the UVA IRB-HSR prior to use. Participants will be given a consent form to review and a member of the study team will be available to answer any questions. Informed consent will be obtained from each participant prior to conducting any study-specific procedures or administering study drug.

10.4 Maintenance of Study Documents

Signed consent forms and other research records will be retained in a confidential manner. Study records will be kept for at least 6 years after completion of the study.

10.5 Compliance with Trial Registration and Results Posting Requirements

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

10.6 Data Collection

Data will be collected using a centralized electronic case report form called **ON**-line **C**linical **O**ncology **R**esearch **E**nvironment = **Oncore**.

10.6.1 Endpoint Data

- Endpoint data will be collected using HITC IML data forms, participant-specific binders, and the HITC laboratory database.

- The HITC laboratory database, which has password-restricted access, is stored on the UVA Health System Computing Services secured server.

10.7 Data Safety Monitoring Plan

The University of Virginia Cancer Center Data and Safety Monitoring Committee (CC DSMC) will provide oversight of the conduct of this study. The CC DSMC will report to the UVA Protocol Review Committee (PRC).

The UVA CC DSMC will review the following:

- All adverse events
- Audit results
- Application of study designed stopping/decision rules
- Whether the study accrual pattern warrants continuation/action
- Protocol violations

10.8 DSMC Monitoring Schedule

The UVA CC DSMC will meet every month for aggregate review of data. Tracking reports of the meetings are available to the PI for review. Issues of immediate concern by the DSMC are brought to the attention of the sponsor (and if appropriate to the PRC and IRB) and a formal response from the sponsor is requested. Per the UVA Cancer Center NIH approved institutional plan, this study will be audited approximately every 6 months.

11.0 APPENDICES

11.1 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.

11.2 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)

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

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

* As published in the European Journal of Cancer:

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

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

11.4 New York Heart Association Disease Classification

Functional Capacity	Objective Assessment
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

* The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256

11.5 Summary of Changes

Version Date	Description of Changes
12-12-17	1) Section 5.1.2: added "cytotoxic" in exclusion criterion 8 to clarify that cytotoxic chemotherapy is an exclusion within 2 weeks prior to day 1. 2) Section 5.2.2: replaced Table 3 with revised Merck provided table "Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab", edited to include language regarding AEs resolving to "grade 0-1 or baseline" under general instructions #2.
10-23-17	1) Table 3: revised to include the phrase "or baseline" under the "All Other Drug-Related Toxicity". This change will allow patients to restart treatment if they resolve to baseline. 2) Section 7.1.2.7.1: clarification--added the phrase "at least one" to the description of core biopsies. This language is now consistent with the biopsy description in section 2.1 of the protocol. 3) Table 6 and Table 9: editorial corrections.
08-25-17	1) Updated list of study personnel. 2) Updated table of contents. 3) Sections 2.1, 4.4.2, 5.1.2 (8)(iii), Table 2, 5.2.1.3.1, : Revised dosing for HDCRT for patients with previously radiated lesions and clarified dosing for lesions that have not been previously radiated versus those lesions that have been previously radiated.. Patients with previously radiated lesions will be treated with 25 Gy in 5 fractions provided that this dose can be administered safely, per the discretion of the treating radiation oncologist. 4) Section 5.2.1.2, 5.2.2: Removed reference to a pharmacy manual and revised to specify that pembrolizumab will be administered per standard clinical practice as we are using commercial drug. 5) Section 5.2.2: Increased the window for administration of pembrolizumab and the biopsy/research blood collections from +/- 2 days to +/- 3 days. Added clinical labs to Table 4 and specified that the collection window for these labs (after Day 1) is +/- 3 days. The +/- 3 day window will provide greater flexibility with scheduling multiple study procedures within a short time frame. 6) Section 5.3: Increased the window for randomization from 7 to 10 days prior to the start of treatment. 7) Section 6.1: • Study Tables for Arm A, B, and C: Added footnote "u" to Day 22 and Day 43 PT/PTT and INR labs. Footnote "u" was amended to specify that the PT/PTT and INR labs should be completed prior to the biopsy.

	• Study Table for Arm C: Added a clinical assessment at Day 15. This assessment is completed as part of clinical care. • Revised footnote "r" to specify that days 4 and 5 of radiation are also required for subjects receiving HDCRT to lesions that were radiated previously. 8) Section 6.2: • Added footnote "d" to cycles 1, 2, 3, PT/PTT and INR labs. Footnote "d" was amended to specify that the PT/PTT and INR labs should be completed prior to the biopsy. 9) Section 7.1.6.2: Revised to clarify that bone scans will be completed per clinical practice for those patients with bone metastases. 10) Section 7.1.2.7.1 (1): Revised to clarify that FFPE samples should ideally be large enough to be able to cut 8-10 slides. Revised to clarify that **on the days when both study intervention and biopsies are scheduled, biopsies should be completed prior to the study intervention.** 11) Section 7.1.3: Revised to clarify that pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Revised to specify that results from the laboratory procedures must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment **or study intervention**.
03-03-17	1) Formatting changes made throughout document. 2) Editorial corrections made throughout document. 3) Updated table of contents 4) Section 5.8: corrected number of doses-changed 35 to 34 because cycle 1 is 6 weeks long rather than 3 weeks long. 5) Section 6.1: Study flow chart-initial treatment phase (Arms A,B,C): a. Moved urinalysis from cycle 3 to cycle 2 to correspond with other testing (e.g. thyroid testing) b. Added footnote "w" to clarify the schedule following cycle 4;footnote "w" was added to the thyroid tests and urinalysis at cycle 5. c. Added an "X" for research bloods at cycle 6 because research bloods following cycle 4 will be drawn on odd and even number cycles. Refer to footnote "t" for timing. d. Corrected footnote "t". Cycle 35 was changed to 34. e. Added a row for disease history to be captured at screening. 6) Section 6.2: Study flow chart-second course treatment a. Added footnote "n" to clarify the schedule following cycle 2; footnote "n" was added to the thyroid tests and urinalysis at cycle 3 7) Table 6: moved LDH from the chemistry panel to the "other" column. LDH is not included in the chemistry panel and will be completed as specified in the study calendars (section 6.0) 8) Table 6: moved direct bilirubin to the "other" column and specified that it will be completed at the time of the chemistry during MK3475 treatment days. The physician wants to have the direct bilirubin drawn on

	treatment days to avoid delays in having to wait for the labs to be re-drawn in infusion if bilirubin is elevated. 9) Section 8.1: corrected doses of pembrolizumab; changed 35 to 34.
01-16-17	1) Page 1: Added IND number (IND131877) to the study document. 2) Revised entry criteria listed under 5.1.1 in response to FDA review of the IND submission: Subjects must have a histologically or cytologically proven advanced solid tumor malignancy for which palliative radiation is recommended. In solid tumors where pembrolizumab has been approved for use, patients may receive pembrolizumab as indicated, in the context of this protocol. In solid tumors where pembrolizumab has not been approved for use, the following criteria apply: • Patients must be resistant to at least 1 prior conventional chemotherapy regimen or other standard of care regimen, • Patient must have no remaining conventional treatment options proven to provide long-term disease control, and • Patient has declined other conventional treatment options Palliative radiation therapy may be recommended for primary tumor and/or any metastatic site that is accessible to biopsy. 3) Revised Section 5.1.2, Exclusion Criteria—deleted #17: Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent. 4) Revised Section 5.1.2, Exclusion Criteria—revised #6 to specify to specify that this exclusion criterion includes prior anti-PD-1, anti-PD-L1 and anti-PD-L2 blockade.
10-12-16	1) Updated Table of Contents 2) Updated Signature Page 3) Section 6.1: Corrected calendar to include Pathology Review at screening for both Arms B and C.
08-16-16	1) Updated Table of Contents 2) In accordance with the update to protocol eligibility criteria received from Merck (correspondence date 25 July 2016), exclusion criterion #12 has been changed to the following: “Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.” 3) Section 6.0: Trial Flow Charts a) Added pathology review to the study tables b) Added symptom diary to the study tables c) Corrected superscript for serum biomarkers (Arm B) d) Made editorial changes to improve readability e) Added text to table header for additional treatments to clarify the

	length of time for each study cycle. f) Added pembrolizumab to the study tables. g) Added a pregnancy test to the second course treatment table and a corresponding footnote "m" to specify timing of completion of the pregnancy test.
07-14-16	1) Editorial corrections were made throughout the study document. 2) Investigator List: Revised to include only the sponsor-investigator, biostatisticians, and CRCs. 3) Table of Contents: Updated 4) Section 1.0: • Updated clinical indication to clarify that the intent is to enroll subjects who require palliative HDCRT. • Editorial correction was made to the Treatment Group, Arm A description. • Estimated duration of the trial was changed from 3 years to 4 years. • Duration of participation was changed from 13 months to 2 years. We revised the study so that all subjects will receive 4 doses of pembrolizumab over the course of 12 weeks. Those subject who have measurable disease (based on RECIST 1.1) outside of the radiation field and who have derived benefit from pembrolizumab may continue to receive pembrolizumab for up to 2 years. • Estimated average length of treatment per patient (about 1 year) was added. 5) Section 2.1: Trial Design • Revised the description of the study drug regimens to specify that all subjects will receive 4 doses of pembrolizumab over the course of 12 weeks. Those subject who have measurable disease (based on RECIST 1.1) outside of the radiation field and who have derived benefit from pembrolizumab may continue to receive pembrolizumab every 3 weeks for up to 2 years. • Revised the language for the biopsies on Day 1 to address tumor sites that have been previously radiated • Revised the tumor assessments to specify that tumor assessments will be completed at screening, Day 85, and then per standard clinical practice based on tumor site, or a minimum of every 12 weeks. • Revised the study schema to match the changes made to the treatment regimens. 6) Section 3.3: Exploratory Objectives—Added the following 2 exploratory objectives: • Describe associations/cross classifications between change in $CD8^+$ T cell and T regulatory cell (T_{reg}) infiltration in tumors. • Summarize clinical outcomes of response, progression-free survival and overall survival

	7) Section 4.2.1: Preclinical Data Evaluating the Effects of HDCRT on Tumor Specific Immune Responses: editorial changes 8) Section 4.4.1: Rationale for the Trial and Selected Subject Population • Revised paragraph 1 in accordance with the revisions made to the inclusion criteria. 9) Section 4.4.2: Rationale for Dose Selection/Regimen Modification • Completed editorial changes to paragraphs 1 and 2. 10) Section 4.4.3.2: Efficacy Endpoints • Revised to include a description of the exploratory objectives. 11) Section 5.1.1: Diagnosis/Condition for Entry into the Trial • Introductory paragraph was revised to specify the following: Subjects must have a histologically or cytologically proven advanced solid tumor malignancy for which palliative radiation is recommended. Patients must have progressed or relapsed after receiving at least one standard systemic therapy and must have no additional curative therapies available. Palliative radiation therapy may be recommended for primary tumor and/or any metastatic site that is accessible to biopsy. • Inclusion criterion 3 was revised to specify that subjects may have disease that is encompassed within the radiation field or may have known disease both inside and outside of the radiation field. • Inclusion criterion 4a: Revised to specify that the Day 1 biopsy is required only if a pre-study biopsy is not available or for subjects who received prior radiation at a tumor site that will be re-radiated as part of the proposed study. • Inclusion criterion 6: Editorial correction was made to the lab value for albumin. • Inclusion criterion 8: Revised to match Merck protocol template v7. • Inclusion criterion 9: Updated to match Merck protocol template v7. 12) Section 5.1.2: Subject Exclusion Criteria • Exclusion criterion 1: moved forward to #1 to specify that subjects will be excluded if they require urgent treatment with cytotoxic chemotherapy or other therapy is indicated (e.g., symptomatic visceral metastases). • Added entry criterion 3 to specify that subjects with a diagnosis of immunodeficiency are excluded. • Exclusion criterion 6: revised to clarify the timing of administration of prior therapies including anti-cancer monoclonal antibodies, growth factors, interferon or interleukin therapy, and other agents with putative immunomodulating activity. • Exclusion criterion 7: revised to clarify the timing of administration of prior allergy desensitization injections and the timing and dose of systemic corticosteroids. • Exclusion criterion 8: revised the third bullet point to specify that

	lesions that have been selected for HDCRT may have been previously radiated provided: i) the tumor site that was previously radiated has progressed and ii) a baseline biopsy of the tumor site is obtained following progression and prior to study entry. • Exclusion criterion 9: added to specify that an additional malignancy that is progressing or requires active treatment is exclusionary with exceptions provided. • Exclusion criterion 11: revised to clarify the criteria for excluding subjects on the basis of an active autoimmune disease. 13) Section 5.2: Trial Treatments; Table 2, Revised dose/frequency and regimen/treatment period for pembrolizumab to clarify treatment options for subjects who have disease that is encompassed within the radiation field and for subjects who have disease both inside and outside of the radiation field. 14) Section 5.2.1.4.1: Dose Modification of Pembrolizumab (Escalation/Titration/Other) • Revised heading to match Merck protocol template v7. • Removed reference to an ECI guidance document. • Table 3: Revised the dose modification guidelines to match Merck template v7. • Editorial changes 15) Section 5.2.2: Table 4: Delayed Visits for Reasons Other Than Toxicity • Revised treatment period to up to 2 years for follow up after early discontinuation for reasons other than disease progression. • Corrected the placement of the reference to the footnote. • Clarified that radiation should be administered on 3-5 consecutive business days. 16) Section 5.5: Concomitant Medications/Vaccinations (allowed and prohibited): Editorial changes were made to the introductory paragraph. 17) Section 5.5.1: Acceptable Concomitant Medications • Editorial changes to change header for permitted medications. 18) Section 5.5.2: Prohibited Concomitant Medications • Revised to clarify that during screening and the treatment phase of the study, stereotactic radiation therapy to up to 3 metastases may be allowed at the investigator's discretion. 19) Section 5.6.1: Supportive Care Guidelines for Pembrolizumab • Removed reference to the ECI guidance document • Revised management plan for diarrhea/colitis to match Merck template v7. 20) Section 5.7.2: Contraception: Revised to match Merck protocol template v7. 21) Section 5.8: Subject Withdrawal/Discontinuation Criteria • Updated link to the section reference. • Reordered list of criteria

	• Revised criteria for completed months of uninterrupted treatment. One year of uninterrupted treatment was changed to 24 months of 35 administrations of study medication, whichever is later. • Revised End of Treatment and Follow-up visit procedures description to match Merck protocol template v7. 22) Section 5.8.1: Treatment after Initial Radiologic Progression • Added this section to describe the criteria for treatment after initial radiologic progression. 23) Section 5.8.2: Discontinuation of Study Therapy after CR (applicable for subjects with disease outside of the radiation field) • Added this section to provide guidance for discontinuing treatment after a confirmed CR and for allowance of a second course phase of treatment at the discretion of the investigator.. 24) Section 6.1: Study Flow Chart • Individual study calendars were made for each study arm. • Study calendar and footnotes were updated—editorial corrections • Prior and concomitant medication review was added as a separate line to the study calendar • Urinalysis was added to Day 64 • The window for pre-study labs (footnote b) was reduced to 10 days. • A footnote was added to all biomarker samples to specify that they will be taken only when available (disease specific). • A separate line was added for tumor imaging along with a footnote to clarify the timing of the imaging. • An additional flow chart was added to specify timing of events for subjects who have active disease outside of the radiation field. • Footnote was revised to clarify the schedule for PT/PTT and INR testing at the time of optional biopsies. • Footnote was added to describe the biopsy requirements. • Footnote was revised to clarify the follow-up schedule for subjects who discontinue pembrolizumab without documented disease progression. • Footnote was added to clarify the timing of collection of AEs, SAEs, and ECIs. • A study flow chart was added for to describe the events for subjects who receive a second course phase of pembrolizumab. • Footnote was added to specify the timing of the collection of research bloods. • Footnote was added to refer to Table 6 for a listing of the required labs. 25) Section 6.2: Study Flow Chart- Second Course Phase • A study table was added for the Second Course Phase

	26) Section 7.1: Trial Procedures: Added hyperlink. 27) Section 7.1.1.1.1: General Informed Consent: Removed the phrase "at the protocol level" from the description of consent form content. 28) Section 7.1.1.6.3: Subsequent Anti-Cancer Therapy Status: Replaced "must" with "should". 29) Section 7.1.2.1: Adverse Event (AE) Monitoring: Deleted paragraph describing evaluation AEs of unknown etiology and ECI attribution to match Merck template v7. 30) Section 7.1.2.6.1: Serum Marker of Disease Activity: Revised to specify that serum markers of disease activity will be collected at the investigators discretion per standard clinical practice. 31) Section 7.1.2.6.2: Tumor Imaging: Revised to specify that the same method of assessment will be used to evaluate tumor burden at baseline and throughout the course of the study. Clarified requirements for imaging. 32) Section 7.1.2.6.3: Tumor Measurements: Revised to clarify how tumor measurements and confirmation scans will be obtained. 33) Section 7.1.3: Table 6: Laboratory Tests: Revised to include footnotes to describe the tests for HIV, HBV, and HCV. 34) Section 7.1.5: Visit Requirements: Hyperlinks were added. 35) Section 7.1.5.3.1: Safety Follow-Up visit: Revised to specify that AEs should resolve to Grade 0-1 or baseline. 36) Section 7.1.5.3.2: Follow-up Visits: Revised to specify timing of follow-up visits and to specify that annual follow-up may be completed by telephone. 37) Section 7.1.5.3.3: Survival Follow-up: revised to change 1 year of therapy to 2 years of therapy. 38) Section 7.1.5.4: Second Course Phase (Retreatment Period): This section has been added to describe second course phase treatment. 39) Section 7.2.1: Time Span for Recording Adverse Events • This section was revised to match the wording from the Merck protocol template v7. 40) Section 7.2.2: Definitions • Some of the language here was moved to section 7.2.1 and revised to match Merck protocol template v7. • Serious AE: language has been added to match Merck protocol template v7. • Additional text was added to the definition of suspected adverse reaction. 41) Section 7.2.3: Attribution Assessment • Additional text was added to Attribution to refer the reader to Table 7 for additional guidance on evaluation of attribution. 42) Table 7: Evaluating Adverse Events • Revised to match Merck protocol template v7. 43) Section 7.2.7: Dose Limiting Toxicities • Revised definition of DLT which takes into account the revised dose modification guidelines for drug-related adverse events (table 3).

	44) Section 7.2.8.4: Reporting to the FDA-revised FDA reporting requirements were updated. 45) Section 7.2.8.5: Reporting of Pregnancy and Lactation to the Sponsor and to Merck: revised to match Merck protocol template v7. 46) Section 7.2.8.7: Immediate Reporting of Adverse Events to the Sponsor and to Merck: revised to match Merck protocol template v7. 47) Section 7.2.8.8: Reporting Events of Clinical Interest • Revised the header for this section • Revised text to match Merck protocol template v7 • Deleted text that referenced a spearte ECI guidance document as the relevant information from the guidance document has been incorporated into the protocol. 48) Section 8.1: Design • Hyperlinks have been corrected. • 17 doses was revised to 35 doses. 49) Section 8.2: Sample Size • DLT definition was moved to section 7.2.7 50) Section 8.3: Safety • Revised to correct hyperlink. • DLT paragraph has been moved. 51) Section 8.4: Analyses: deleted the term “prostate” as many solid tumors will be analyzed as part of this study. 52) Table 13: numbering was corrected and the table was changed to Table 11.
10-19-15	1) Corrected page number in table of contents for section 5.2.2 2) Moved PT/PTT and INR from day 1 to screening as it is an inclusion criteria
10-01-15	1) Section 5.1.2: (7): Added text that excluded subjects who had untreated brain metastases, brain metastases that were retreated, or subjects whom have either midline shift, or any signs of herniation (even if disease has been treated with Gamma Knife). Clarified that subjects with brain metastases must have completed CNS radiation at least 10 days prior to study treatment. 2) Minor formatting changes
09-28-15	1) Section 5.6.1: The phrase “or Grade 2 diarrhea” was added to the management of diarrhea/colitis section of the protocol. This phrase was omitted in error in prior versions of the protocol.
09-24-15	1) Updated Table of Contents 2) Section 5.1.2 (5c): Removed the text that permitted gamma knife or stereotactic radiosurgery administration within 2 weeks prior to beginning study therapy. This change was based on the outcome of the PRC review and concerns of a CNS flare (immune

	pseudoprogression) following treatment.

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