TITLE: Phase II Study for the Evaluation of Efficacy of Pembrolizumab (MK-3475) in Patients with Rare Tumors

PRINCIPAL INVESTIGATOR: Aung Naing, MD

SUPPORTER and DRUG SUPPLY:
Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Supporter or Merck)
One Merck Drive
P.O. Box 100
Whitehouse Station, NJ 08889-0100, U.S.A.

SPONSOR (IND Holder):
The University of Texas MD Anderson Cancer Center
(hereafter referred to as the MDACC IND or Sponsor)
Aman Buzdar, M.D.
Vice President for Clinical Research Administration
University of Texas M. D. Anderson Cancer Center
1515 Holcombe Blvd., Unit 1636
Houston, TX 77030

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1.0 TRIAL SUMMARY

Abbreviated Title	Phase II Pembrolizumab (MK-3475) in Rare Tumors
Trial Phase	II
Clinical Indication	Subjects will be enrolled into one of the following 10 tumor cohorts: 1) Squamous cell carcinoma of the skin 2) Anaplastic thyroid cancer 3) Adrenocortical carcinoma 4) Medullary renal cell carcinoma 5) Carcinoma of unknown primary 6) Penile carcinoma 7) Thymoma 8) Testicular carcinoma 9) Paraganglioma-pheochromocytoma 10) Other rare tumor histologies
Trial Type	Interventional
Type of control	No Treatment Control
Route of administration	Intravenous
Trial Blinding	Unblinded, Open-Label
Treatment Groups	Pembrolizumab (MK-3475) 200 milligrams intravenous infusion every 3 weeks
Number of trial subjects	250 Subjects
Estimated enrollment period	March 2016-April 2018
Estimated duration of trial	The investigator estimates that the trial will require approximately 24 months from the time the first subject signs the informed consent until the last subject's last visit
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact. After a screening phase of 28 days, eligible subjects will receive treatment on Day 1 of each 21 day dosing cycle. Treatment with pembrolizumab (MK-3475) will continue until documented confirmed disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements; subject receives 24 months of study medication, or administrative reasons. Subjects who attain a complete response may consider stopping trial treatment if they meet criteria for holding therapy. Subjects who stop trial treatment after receiving 24 months of study medication for reasons other than disease progression or intolerability or who attain a complete response and stop trial treatment may be eligible for up to one year of retreatment after experiencing disease progression. The decision to retreat will be at the discretion of the investigator only if they meet the criteria for retreatment and the trial is ongoing. After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (study drug-related serious adverse events will be collected for 90 days after the end of treatment). Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up.

	All subjects will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a single-center, open-label, phase II trial of pembrolizumab (MK-3475) in patients with and without programmed death-ligand 1 (PD-L1) positive advanced tumors to be conducted at the University of Texas MD Anderson Cancer Center.

Participation in this trial will be dependent upon pathology or histologic confirmation of an advanced tumor type. Subjects will be enrolled into one of the following 10 tumor cohorts:

1) Squamous cell carcinoma of the skin
2) Anaplastic thyroid cancer
3) Adrenocortical carcinoma
4) Medullary renal cell carcinoma
5) Carcinoma of unknown primary
6) Penile carcinoma
7) Thymoma
8) Testicular carcinoma
9) Paraganglioma-pheochromocytoma
10) Other rare tumor histologies.

In Cohort 10, "Other rare tumor histologies," the following tumor types will be excluded: melanoma, non-small cell lung cancer, hepatocellular carcinoma, Merkel cell carcinoma, colon or rectal adenocarcinoma, anal canal squamous cell carcinoma, pancreas adenocarcinoma, esophageal squamous cell carcinoma or adenocarcinoma (including GE junction), biliary tract adenocarcinoma (gallbladder and biliary tree but excluding ampulla of vater cancers), carcinoid tumors, neuroendocrine carcinomas (well or moderately differentiated pancreatic neuroendocrine tumor), ER-positive HER2-negative breast cancer, triple negative breast cancer, ovarian epithelial, fallopian tube or primary peritoneal carcinoma, endometrial carcinoma, cervical squamous cell cancer, vulvar squamous cell carcinoma, small cell lung cancer, malignant pleural mesothelioma, thyroid cancer (papillary or follicular subtype), salivary gland carcinoma, nasopharyngeal carcinoma, glioblastoma multiforme, leiomyosarcoma, prostate adenocarcinoma, gastric adenocarcinoma, and small bowel malignancy.

Patients will be enrolled regardless of their PD-L1 expression status. Patients will supply tissue from an archival tissue sample or newly obtained biopsy (if archival tissue is not available) of a tumor lesion not previously irradiated (tumors progressing in a prior site of radiation are allowed for PD-L1 characterization, other exceptions may be considered after PI consultation). This specimen will be evaluated at a central laboratory for expression status of PD-L1 by immunohistochemistry (IHC).

Toxicities will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Subjects will be evaluated every 3 cycles

= every 9 weeks (63 days ±7 days) with radiographic imaging to assess response to treatment. Response Evaluation Criteria in Solid Tumors (RECIST) 1.1[1] will be used as the primary efficacy endpoint of response rate.

Treatment with pembrolizumab (MK-3475) will continue until documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, completion of 24 months of treatment with pembrolizumab (MK-3475), or administrative reasons. Subjects who attain an investigator-determined confirmed complete response (CR) may consider stopping trial treatment after receiving at least 27 weeks (9 cycles) of treatment. In addition, subjects who discontinue after at least 24 months of therapy for reasons other than disease progression or intolerability, or who discontinue after attaining a CR and had at least 2 treatments beyond initial CR, may be eligible for up to one year of retreatment if they subsequently experience radiographic disease progression. The decision to retreat will be at the discretion of the investigator only if no cancer treatment was administered since the last dose of pembrolizumab (MK-3475), the subject still meets the safety parameters listed in the Inclusion/Exclusion criteria and the trial remains open. After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (study drug-related serious adverse events will be collected for 90 days after the end of treatment). Subjects who discontinue treatment for reasons other than disease progression will have post-treatment follow-up of disease status until disease progression, or initiating a non-study cancer treatment, or withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone contact for overall survival until death, withdrawal of consent or the end of the study, whichever comes first.

Immunotherapeutic agents such as pembrolizumab (MK-3475) may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions. If initial radiologic imaging shows progressive disease (PD), tumor assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing treatment per below 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.

The primary objective of the trial is to evaluate efficacy by evaluation of non-progression rate (NPR) at 27 weeks (9 cycles) as defined as the percentage of patients who are alive and progression-free at 27 weeks (9 cycles)as assessed by RECIST 1.1, of pembrolizumab (MK-3475) in subjects with or without PD-L1 positive advanced tumors. Secondary objectives include evaluating safety and tolerability of pembrolizumab (MK-3475); correlating efficacy, non-progression rate (NPR) at 27 weeks (9 cycles), objective

response (CR or PR), progression-free survival (PFS), overall survival (OS) and duration of response (DOR) to PD-L1 status; and identifying imaging characteristics associated with immunological changes in tumor following treatment with pembrolizumab.

2.2 Trial Diagram

The trial design is depicted in Figure 1.

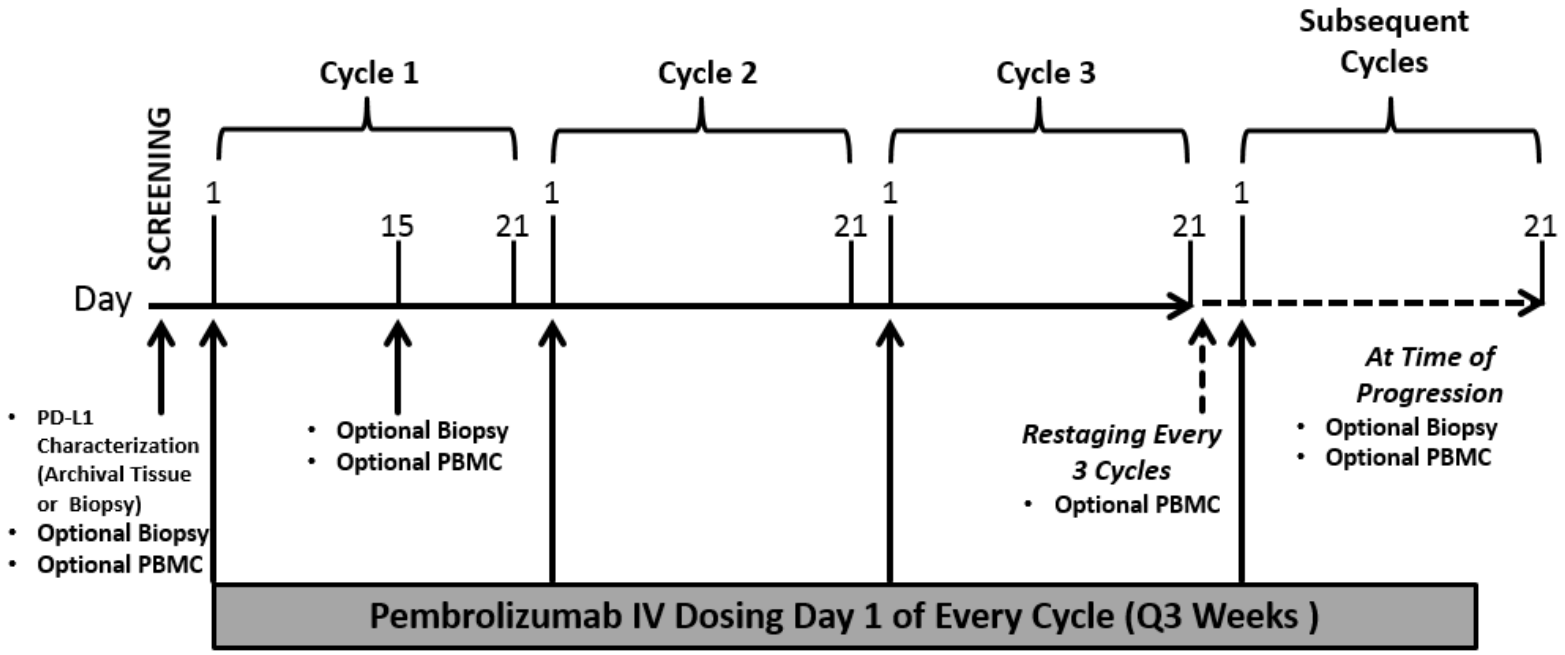

Figure 1: Dosing and Optional Correlative Schema
Patients will be co-enrolled on other protocols in which the PBMC and tissue samples will be utilized for analyses.

3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objective

Objective: To obtain early indication of efficacy by evaluation of non-progression rate (NPR) at 27 weeks as defined as the percentage of patients who are alive and progression-free at 27 weeks as assessed by RECIST in patients with advanced tumor types receiving pembrolizumab.

3.1.1 Secondary Objectives

(1) **Objective**: To correlate efficacy by evaluation of tumor size to PD-L1 status among patients with advanced tumor types receiving pembrolizumab.

(2) **Objective:** To evaluate safety and tolerability of pembrolizumab in patients with advanced tumors.

(3) **Objective:** To evaluate the percentage of patients with objective response (CR or PR), progression free survival (PFS), overall survival (OS), and duration of response (DOR) in patients with advanced tumor types receiving pembrolizumab.

(4) **Objective:**To evaluate the NPR at 27 weeks (9 cycles), objective response (CR or PR), PFS, and DOR as assessed by irRECIST in patients with advanced tumor types receiving pembrolizumab.

(5) **Objective:** To correlate the NPR at 27 weeks (9 cycles), objective response (CR or PR), PFS, OS, and DOR to PD-L1 status among patients with advanced tumor types receiving pembrolizumab.

3.1.2 Exploratory Objectives:

(1) **Objective:** To evaluate the potential role of tumor-associated immune biomarkers for prediction of therapy effectiveness in patients with advanced tumor types receiving pembrolizumab.

(2) **Objective:** To correlate the potential role of tumor-associated immune biomarkers for prediction of therapy effectiveness to PD-L1 status among patients with advanced tumor types receiving pembrolizumab.

(3) **Objective:** To identify imaging characteristics associated with immunological changes in tumor following treatment with pembrolizumab.

(4) **Objective:** To compare tumor mutation burden and serial assessment of mutation status in biopsies obtained at baseline and progression in patients with advanced tumor types receiving pembrolizumab.

3.2 Hypotheses:

Intravenous administration of single agent pembrolizumab (MK-3475) to subjects with a given PD-L1 positive advanced tumor type will result in an NPR at 27 weeks (9 cycles) greater than 20% based on RECIST 1.1 criteria.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on pembrolizumab (MK-3475).[2]

4.1.1 Pharmaceutical and Therapeutic Background

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

The programmed death 1 (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.

4.1.2 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for Preclinical and Clinical data.[2]

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Intact immune surveillance plays a significant role in controlling development of neoplastic transformation.[3] PD-1 is an immune-checkpoint receptor expressed by T cells. PD-L1 is expressed in the tumor microenvironment of various cancers. Upon binding to either of its ligands, PD-L1 or PD-L2, the PD-1 pathway negatively regulates T-cell effector functions. Increased expression of PD-L1 and an immunosuppressive microenvironment are associated with ineffective host immune response and subsequent disease progression in multiple tumor malignancies. There is a strong correlation between presence of effective lymphocytes and favorable prognosis in different types of malignancies.[4-6] Tumors take advantage of immune check points such as the PD-1/PD-L1 pathway to evade immune destruction, resulting in disease progression.[7,8] To overcome tumor immune suppression and to establish an effective antitumor immune response, it is necessary to overcome multiple immunosuppressive mechanisms.[9,10] Anti-PD1, anti-PD-L1, and anti-CTLA-4 are designed to block immune checkpoints. These checkpoint inhibitors thereby decrease immune suppression and increase the antitumor effect.

Pembrolizumab (also known as lambrolizumab and previously known as MK-3475) 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. The t1/2 of pembrolizumab is approximately 2-3 weeks (14-21 days), and with no indication

of dose dependency of half-life among three dose groups (1, 3, and 10 mg/kg), which supports a dosing interval of every 2 or 3 weeks.[11] Steady-state trough concentrations were 20% greater in patients receiving 10 mg/kg every 2 weeks than in those receiving the same dose every 3 weeks. Pembrolizumab has shown overall response rates of approximately 38% in patients with melanoma and ~20% in patients with non-small cell lung cancer. In September 2014, the FDA granted early approval for pembrolizumab in melanoma patients with BRAF V600 mutation following ipilimumab therapy.[12]

Currently, a single agent pembrolizumab trial is being conducted in over 20 PD-L1 expressing tumors including: colon or rectal adenocarcinoma, anal canal squamous cell carcinoma, pancreas adenocarcinoma, esophageal squamous cell carcinoma, adenocarcinoma (including GE junction), biliary tract adenocarcinoma (gallbladder and biliary tree but excluding ampulla of vater cancers), carcinoid tumors, neuroendocrine carcinomas (well or moderately differentiated pancreatic neuroendocrine tumor), ER+/HER2-negative breast cancer, ovarian epithelial, fallopian tube or primary peritoneal carcinoma, endometrial carcinoma, cervical squamous cell cancer, vulvar squamous cell carcinoma, small cell lung cancer, mesothelioma (malignant pleural mesothelioma), thyroid cancer (papillary or follicular subtype), salivary gland carcinoma, nasopharyngeal carcinoma, glioblastoma multiforme, leiomyosarcoma, prostate adenocarcinoma (NCT02054806).

Progress is unfolding in the understanding of how the immune system can modulate tumor progression or effective responses against cancer.[13] In some studies, the levels of PD-L1 expression have correlated with clinical outcome.[14-16] However, the prognostic impact of PD-L1 expression still needs to be defined in rare tumor types.

Our strategy for this study is to focus on advanced rare types with and without PD-L1-expressing tumors. We will exclude all types of tumors that are enrolled in the current Phase1B study of MK-3475-028 (NCT02054806). In this study, our goal is to characterize the presence of PD-L1 expression in advanced tumor tissues and to correlate levels of PD-L1 expression with clinico-pathological features as well as survival outcomes.

4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

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

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

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

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

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

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The primary objective of this study is to evaluate the efficacy by evaluation of non-progression rate (NPR) at 27 weeks as defined as the percentage of patients who are alive and progression-free at 27 weeks as assessed by RECIST, of pembrolizumab (MK-3475) in subjects with and without PD-L1 positive advanced tumors. Response rates per RECIST 1.1 will be evaluated. RECIST 1.1[1] as assessed by the investigator will be used as the primary response rate efficacy endpoint. RECIST 1.1 will also be used by the local site to determine eligibility and make treatment decisions. Response for secondary objectives will be determined by irRECIST compared with those of derived using RECIST 1.1.

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab (MK-3475). Immunotherapeutic agents such as pembrolizumab (MK-3475) may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab (MK-3475). Therefore, RECIST 1.1 will be used with the following adaptations:

- If radiologic imaging shows initial PD, tumor assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing treatment per below 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 / resumed. If repeat imaging confirms progressive disease, subjects will be discontinued from study therapy (exception noted in Section 7.1.2.6). In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions.

In subjects who have initial evidence of radiological PD, it is at the discretion of the treating physician whether to continue a subject on study treatment until repeat imaging is obtained a minimum of 4 weeks later. This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive pembrolizumab (MK-3475) treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms 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.

When feasible, subjects should not be discontinued until progression is confirmed. This

allowance to continue treatment despite initial radiologic progression takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation of progressive disease.

4.2.3.2 Safety Endpoints

The secondary safety objective of this study is to characterize the safety and tolerability of pembrolizumab (MK-3475) in subjects with or without PD-L1 positive advanced tumors. The safety analysis will be based on subjects who experienced toxicities as defined by CTCAE criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab (MK-3475), including serious adverse events (SAEs) and events of clinical interest (ECIs).

Safety will be assessed by reported adverse experiences using CTCAE, Version 4.03. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific immune-related adverse events (irAEs) will be collected and designated as immune-related events of clinical interest (ECIs) as described in Section 7.2.3.2.

Patients enrolled on this study will be approached for co-enrollment on PA15-0315 prospective study to assess immune-related adverse events when receiving immunotherapy at the University of Texas MD Anderson Cancer Center (Aung Naing, MD). All samples and scans will be collected using procedures characterized in this protocol, and all patients will be consented for procedures done under this optional protocol separately.

4.2.3.3 Biomarker Research

Additional biomarker research to identify factors important for pembrolizumab (MK-3475) therapy will also be pursued. For example, tumor and blood samples from this study may undergo proteomic, genomic and transcriptional analyses. Additional research may evaluate factors important for predicting responsiveness or resistance to pembrolizumab (MK-3475) therapy and other immunologic targets.

Participation in this trial will be dependent upon supplying tissue from an archival tissue sample or newly obtained biopsy (if archival tissue is not available) of a tumor lesion not previously irradiated (tumors progressing in a prior site of radiation are allowed for PD-L1 characterization, other exceptions may be considered after PI consultation). This specimen will be evaluated at a central laboratory for expression status of PD-L1 by immunohistochemistry (IHC). Optional baseline, on-treatment and time of progression (if patients have had CR/PR/or SD for > 27 weeks) biopsies will be obtained for evaluation of the potential role of tumor-associated immune biomarkers for prediction of therapy effectiveness.

Peripheral blood mononuclear cell (PBMC) will be collected as an optional procedure at baseline, tumor restaging, in conjunction with optional biopsies, and time of progression (if patients have had CR/PR/or SD for > 27 weeks). These samples will be sent to a central laboratory at Merck for the NanoString assay that will evaluate immune-related gene expression signatures and the potential to predict benefit from pembrolizumab.

Patients enrolled in this study will be approached for co-enrollment on PA11-0852 Clearinghouse protocol at the University of Texas MD Anderson Cancer Center (Funda Meric-Bernstam, MD) to assess tumor mutation burden and genomic alterations detected in cfDNA. As per the PA11-0852 Clearinghouse protocol, the optional tumor biopsies from baseline and the time of progression (if progression after response or unexpected rapid progression), and serial plasma samples will be analyzed. Development of new mutations or reversal of the mutations will be analyzed and correlated with clinical response. This will be our exploratory objective and no formal statistical analysis will be done.

5.0 SUBJECT ELIGIBILITY

5.1 Study Population

5.1.1 Diagnosis/Condition for Entry into the Trial

Male and female subjects with or without PD-L1 positive advanced tumor (as specified in Section 5.1.2) of at least 18 years will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

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

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

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

3. Have measurable disease based on RECIST 1.1. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

4. Have one of the following advanced (unresectable and/or metastatic) solid tumor indications, that has progressed following standard therapies, where standard therapies are available:

    1) Squamous cell carcinoma of the skin
    2) Anaplastic thyroid cancer
    3) Adrenocortical carcinoma
    4) Medullary renal cell carcinoma
    5) Carcinoma of unknown primary
    6) Penile carcinoma
    7) Thymoma
    8) Testicular carcinoma
    9) Paraganglioma-pheochromocytoma
    10) Other rare tumor histologies (except those tumor types listed in 5.1.3.)

5. Have failed prior treatment within 6 months of consent date.

6. Have biopsiable disease. Subjects must have at least one lesion amenable to biopsy. Tumor lesions used for biopsy should not be lesions used as RECIST target lesions.

7. Be willing to provide archival tissue. If archival tissue is not available, a newly obtained core or excisional biopsy of a tumor lesion will be obtained. Newly-obtained is defined

as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1.

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

9. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 28 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,000 /mcL
Platelets	≥75,000 / 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.	

10. 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.

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

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

5.1.3 Subject Exclusion Criteria

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

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

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

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

4. Hypersensitivity to pembrolizumab or any of its excipients.

5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

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

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

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

7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer, and diseases for which the treatment could reasonably include Pembrolizumab and are not part of the excluded tumor type list or not eligible for the phase I trial.

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

steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

9. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of Pembrolizumab. Note: corticosteroids given within 24 hours of an imaging study for purposes of pre-medication in patients with hypersensitivity to radiologic contrast agents are allowed.

10. Has known history of, or any evidence of active, non-infectious pneumonitis.

11. Has an active infection requiring systemic therapy.

12. 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.

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

14. 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.

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

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

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

18. 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.

19. Is participating in Cohort 10 and has melanoma; non-small cell lung cancer; hepatocellular carcinoma; Merkel cell carcinoma; colon or rectal adenocarcinoma; anal canal squamous cell carcinoma; pancreas adenocarcinoma; esophageal squamous cell carcinoma or adenocarcinoma (including GE junction); biliary tract adenocarcinoma (gallbladder and biliary tree but excluding ampulla of vater cancers); carcinoid tumors;

neuroendocrine carcinomas (well or moderately differentiated pancreatic neuroendocrine tumor); ER-positive HER2-negative breast cancer; triple negative breast cancer; ovarian epithelial, fallopian tube or primary peritoneal carcinoma; endometrial carcinoma; cervical squamous cell cancer; vulvar squamous cell carcinoma; small cell lung cancer; mesothelioma (malignant pleural mesothelioma); thyroid cancer (papillary or follicular subtype); salivary gland carcinoma; nasopharyngeal carcinoma; glioblastoma multiforme; leiomyosarcoma; prostate adenocarcinoma; gastric adenocarcinoma; or small bowel malignancy.

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2. One treatment cycle consists of 3 weeks (21 days) of treatment. Pembrolizumab will be given via intravenous (IV) infusion on Day 1 of every cycle. Patients will be restaged at the end of every three cycles (9 weeks). Patients may be allowed to continue treatment after restaging if there is continued clinical response or disease stabilization and patients do not have significant toxicities.

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab (MK-3475)	200 mg	Q3W	IV Infusion	Day 1 of each 21-Day Cycle	Experimental
The pembrolizumab (MK-3475) dosing interval may be withheld due to toxicity as described in Section 5.2.1.2.					

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 trial treatments in accordance with the protocol and any applicable laws and regulations.

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.

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

5.2.1.2 Dose Modification

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-

related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.6.1 for supportive care guidelines, including use of corticosteroids.

For subjects whose dose was withheld due to toxicity, subjects may resume pembrolizumab (MK-3475) upon resolution of toxicity to Grade 0-1 or baseline. This dose would be considered Day 1 of the next cycle and should be in alignment with the new schedule.

Table 3 Dose Modification Guidelines for Drug-Related Adverse Events

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

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

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

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

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

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

5.2.2 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each 21-day cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab (MK-3475) 200 mg will be administered as a 30 minute IV infusion every 3 weeks (21 days). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

5.2.3 Continuing Study Drug Administration after Initial Evidence of Radiologic Disease Progression

Immunotherapeutic agents such as pembrolizumab (MK-3475) may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

If initial radiologic imaging shows PD, tumor assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing treatment per below 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 (exception noted in Section 7.1.2.5.1). In determining whether or not the tumor burden has increased or decreased, Investigators should consider all target lesions as well as non-target lesions (please refer to the Procedures Manual).

When feasible, subjects should not be discontinued until progression is confirmed; however, the decision to continue study treatment after the 1st evidence of disease progression is at the

Investigator's discretion based on the clinical status of the subject as described in Table 4 below. 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.

Table 4 Imaging and Treatment After 1st Radiologic Evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
1st radiologic evidence of PD	Repeat imaging at ≥4 weeks to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory scan	Repeat imaging at ≥4 weeks to confirm PD if possible	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment (exception noted in Section 7.1.2.5)	No additional imaging required	N/A
Repeat scan shows SD, PR or CR	Continue regularly scheduled imaging assessments every 9 weeks	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments every 9 weeks	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion

5.2.4 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

Subjects participating in this trial will be allocated by non-random assignment.

5.4 Stratification

No stratification based on age, gender, or other characteristics will be used in this trial.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

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.

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the electronic medical record (EMR) including all prescription, over-the-counter (OTC), 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 EMR.

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 if associated with 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 (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.

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

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

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

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. 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** that persists greater than 3 days, administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

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

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

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

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

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

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

Table 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 promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

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

start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

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

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

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the IND Sponsor and to Merck without delay and within 24 hours to the IND 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 IND 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 IND Sponsor and to Merck and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

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

violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4 – Other Procedures.

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

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

  Note: For unconfirmed radiographic disease progression, please see Section 7.1.2.5.

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 7.1.2.5.
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 96 administrations of study medication, whichever is later.

  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.5
- Administrative reasons

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

will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

If a patient has not received 3 doses of study drug, they will be considered inevaluable and will be replaced.

5.8.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 27 weeks (9 cycles) with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.5.5.

5.9 Subject Replacement Strategy

Additional subjects may be enrolled in a given cohort to ensure that the required number of evaluable subjects in each cohort is achieved. A subject that discontinues the trial for progressive disease or a drug-related AE will not be replaced and will be counted in the evaluable population of subjects for the respective cohort.

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 a particular cohort 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

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**								**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	To be repeated beyond 8 cycles[a]				Discon	Safety Follow-up	Follow-up Visits[c]	Survival Follow-up
						5	6	7	8				
Scheduling Window (Days):	-28 to -1	Day 1 (-3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	At time of Discon	30 days from last dose (± 7 days)	Every 9 weeks post discon (± 7 days)	Every 12 weeks (± 4 weeks)
Administrative Procedures													
Informed Consent[b]	X[b]												
Inclusion/Exclusion Criteria	X												
Demographics and Medical History	X												
Concomitant Medication Review	X[d]	X	X	X	X	X	X	X	X	X	X[d]	X	
Trial Treatment Administration[a]		X	X	X	X	X	X	X	X				
Post-study Anticancer Therapy Status												X	X
Survival Status													X
Clinical Procedures/Assessments													
Review Adverse Events[e]	X	X	X	X	X	X	X	X	X	X	X[e]	X[e]	
Physical Examination[f]	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs and Weight[g]	X	X[g]	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	X[h]	X[h]	X[h]	X	X	X	
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory													
Pregnancy Test – Urine or Serum β-HCG[i]	X[i]	X	X	X	X	X	X	X	X	X			
PT/INR and aPTT	X[j]	As Clinically Indicated											
CBC with Differential[k]	X[j]	X[k]	X	X	X	X	X	X	X	X	X[n]	X	

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**								**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	To be repeated beyond 8 cycles[a]				Discon	Safety Follow-up	Follow-up Visits[c]	Survival Follow-up
						5	6	7	8				
Scheduling Window (Days):	-28 to -1	Day 1 (-3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	At time of Discon	30 days from last dose (± 7 days)	Every 9 weeks post discon (± 7 days)	Every 12 weeks (± 4 weeks)
Comprehensive Chemistry Panel[k]	X[j]	X[k]	X	X	X	X	X	X	X	X	X[n]	X	
Urinalysis[k,l]	X[j]			X[l]			X[l]				X[n]		
T3, FT4 and TSH[k]	X[j]			X[l]			X[l]				X[n]		
Tumor Marker Assessment (if available) [m]	X			X[m]			X[m]			X[m]		X[m]	
Efficacy Measurements													
Tumor Imaging[a,o, p, q]	X			X			X			X[q]		X[c]	
Correlative Studies													
Tissue Collection for PD-L1 Characterization[r]	X[r]												
Optional Tumor Biopsy Tissue Collection	X[s]	X[s]								X[s]			
Optional PBMC Collection[t]	X	X[t]		X			X			X[t]			
Immune-related Imaging	X[u]			X[u]			X[u]			X[u]			

a. Treatment cycles are 3 weeks (21 days). Radiographic imaging should be performed every 9 weeks (3 cycles or 63 days ± 7 days) regardless of any treatment delays (i.e. Screening visit, after to Cycle 3, Cycle 6, Cycle 9 and then every 3 cycles (9 weeks)).

b. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 28 days prior to the first dose of trial treatment). Baseline number will be assigned when the study informed consent is signed.

c. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 9 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first.

d. Prior medications – Record all medications taken 28 days before the first dose of trial treatment. Concomitant medications – Enter new medications started during the trial and 30 days after last dose of trial treatment regardless of when the Safety Follow-up visit occurs.

e. Patients enrolled on this study will be approached for co-enrollment on PA15-0315 prospective study to assess immune-related adverse events when receiving immunotherapy All samples and scans will be collected using procedures characterized in this protocol and all patients will be consented for procedures done under this optional protocol separately. Record all AEs occurring within 30 days after the last dose of trial treatment regardless of when the Safety Follow-up visit occurs. After 30 days, record all SAEs (related and unrelated to trial treatment) / ECIs occurring up to 90 days after the last dose of trial treatment or the start of new anti-cancer treatment, whichever comes first. Afterwards, any drug related AE regardless of seriousness occurring outside

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**								**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	To be repeated beyond 8 cycles[a]				Discon	Safety Follow-up	Follow-up Visits[c]	Survival Follow-up
						5	6	7	8				
Scheduling Window (Days):	-28 to -1	Day 1 (-3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	At time of Discon	30 days from last dose (± 7 days)	Every 9 weeks post discon (± 7 days)	Every 12 weeks (± 4 weeks)

of any reporting timeframes must be reported

f. Physical exams are to be completed at screening, Day 1 of every Cycle, End of Treatment, Safety Follow-up and every 9 –week Follow-up visits.

g. Height will be measured at visit 1 only.

h. Following Cycle 8, the ECOG performance status should be determined only in conjunction with a protocol-specified full or directed physical exam (Cycle 9, 11, 13, 15, 17, 19 and every 2 cycles thereafter.

i. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.

j. Laboratory tests for screening are to be performed within 28 days prior to the first dose of trial treatment.

k. After Cycle 1, lab samples can be collected up to 72 hours (3 days) prior to the scheduled time point.

l. Urinalysis and T3, FT4 and TSH are to be repeated every 3 cycles at the time of restaging. If the urinalysis is abnormal, a microscopic urinalysis will be performed.

m. Tumor marker assessment is not an additional study-related laboratory evaluation. The purpose is to collect information that may be a part of standard clinical assessment for certain tumor types. Data collection (if applicable and if available) should occur every 9 weeks (3 cycles or 63 days ± 7 days) regardless of any treatment delays (i.e. Screening visit, after to Cycle 3, Cycle 6, Cycle 9 and then every 3 cycles (9 weeks) thereafter coinciding with imaging visits). Upon discontinuation, tumor marker data collection will occur every 9 weeks coinciding with post-treatment imaging follow-up visits.

n. Unresolved abnormal labs that are drug related AEs should be followed until resolution.

o. The initial tumor imaging will be performed within 28 days prior to the first dose of trial treatment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the first dose of trial treatment. On-study imaging will be performed every 9 weeks (± 7 days) after the first dose of trial treatment and should follow calendar days and should not be adjusted for delays in cycle starts or withholding of pembrolizumab (MK-3475) cycle frequencies. The same imaging technique should be used in a subject throughout the trial. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management. Tumor imaging and assessment per local standard of care should be performed for patient management, and may include additional imaging (e.g. bone scan for prostate cancer patients) and appropriate tumor markers.

p. Per the modified RECIST 1.1 used in this protocol, if imaging shows progressive disease, the imaging assessment should be repeated at a minimum of 4 weeks later in order to confirm progressive disease.

q. If a scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation isn't mandatory. In subjects who discontinue study therapy without confirmed disease progression, a radiological evaluation should be repeated at the time of treatment discontinuation (i.e. date of discontinuation ± 4 week window).

r. Mandatory archived or newly obtained (within 42 days (6 weeks)) FFPE (formalin-fixed paraffin embedded) block or 20 unstained (5 micron) slides must be submitted for characterization at a central lab for PD-L1 characterization. Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1. Tumor lesions not previously irradiated must be provided (tumors progressing in a prior site of radiation are allowed for PD-L1 characterization).

s. Optional tumor tissue will be obtained pre- treatment (baseline), between Cycle 1 Day 15 and Cycle 1 Day 21, and at progression (if patient had CR, PR or SD > 27 weeks) provided there is technically biopsiable tumor, and it is safe for patient to undergo biopsy.

t. Peripheral blood mononuclear cell (PBMC) will be collected as an optional procedure at baseline, tumor restaging, in conjunction with optional biopsies, and time of progression (if patients have had CR/PR/or SD for > 27 weeks). If patients do not opt for the optional tumor biopsies, the optional PBMCs will be collected at baseline, restaging, and time of progression (if patients have had CR/PR/or SD for >27 weeks.

Trial Period:	**Screening Phase**	**Treatment Cycles[a]**								**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	To be repeated beyond 8 cycles[a]				Discon	Safety Follow-up	Follow-up Visits[c]	Survival Follow-up
						5	6	7	8				
Scheduling Window (Days):	-28 to -1	Day 1 (-3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	At time of Discon	30 days from last dose (± 7 days)	Every 9 weeks post discon (± 7 days)	Every 12 weeks (± 4 weeks)

u. The CT or MRI tumor scans for tumor assessment will be utilized for immune-related imaging correlatives. Additional scans will not be required.

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

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 at the protocol level.

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

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

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

7.1.1.4.2 Concomitant Medications

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

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

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

7.1.1.5.2 Prior Treatment Details

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

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

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

7.1.1.6 Assignment of Screening Number

Consented subjects will not be given a unique screening number for randomization or allocation. All patients who meet eligibility criteria and are enrolled in this trial will be registered in Clinical Oncology Research Database (CORe) at the University of Texas MD Anderson Cancer Center at Houston. Each patient will have a CORe accession number.

7.1.1.7 Assignment of Randomization Number

Subjects participating in this trial will be allocated by non-random assignment; therefore, a randomization number will not be assigned to patients.

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

Interruptions from the protocol specified treatment plan for greater than 12 weeks between pembrolizumab (MK-3475) doses due to toxicity require consultation between the investigator and the IND Sponsor and written documentation of the collaborative decision on subject management.

Administration of trial medication will be witnessed by the investigator and/or trial staff. The total volume of trial treatment infused will be compared to the total volume prepared to determine compliance with each dose administered.

The instructions for preparing and administering pembrolizumab (MK-3475) will be provided in the Pharmacy Manual.

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 4.03 (see Section 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs).

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

7.1.2.2 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 physical exam should be performed during screening, Day 1 of every Cycle, End of Treatment, Safety Follow-Up, and every 9-week Follow-up Visit. After the first dose of trial treatment, new clinically significant abnormal findings should be recorded as AEs.

7.1.2.3 Vital Signs

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

7.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

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

7.1.2.5 Tumor Imaging and Assessment of Disease

RECIST 1.1 will be applied by the site as the primary measure for assessment of tumor response and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of study therapy).

RECIST 1.1 will be adapted as follows to account for the unique tumor response seen in this class of therapeutics. If imaging shows PD, tumor assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing treatment for clinically stable subjects as discussed below in Table 6. Clinically stable is defined by the following criteria:

- Absence of signs and symptoms 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.

Table 6 Imaging and Treatment after 1st Radiologic Evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment

1st radiologic evidence of PD	Repeat imaging at ≥ 4 weeks to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory scan	Repeat imaging at ≥ 4 weeks to confirm PD if possible	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment (exception noted in Section 7.1.2.5.)	No additional imaging required	N/A
Repeat scan shows SD, PR or CR	Continue regularly scheduled imaging assessments every 9 weeks	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments every 9 weeks	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion

In determining whether or not the tumor burden has increased or decreased, Investigators should consider all target lesions as well as non-target lesions (please refer to the Procedures Manual). Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation. If radiologic progression is confirmed, then the subject will be discontinued from trial treatment. If radiologic progression is not confirmed, then the subject should resume/continue trial treatment and have their next scan according to the every 9 weeks (63 days ±7 days).

NOTE: If a subject with confirmed radiographic progression (i.e. 2 scans at least 28 days apart demonstrating progressive disease) is clinically stable or clinically improved, and there is no further increase in the tumor dimensions at the confirmatory scan, an exception may be considered to continue treatment upon consultation with the IND Sponsor. Clinically stable subjects should also have at the confirmatory scan no further increase in the target lesions, no unequivocal increase in non-target lesions, and no additional new lesions develop (non-worsening PD) to continue study treatment.

Imaging during the follow-up period is to be repeated every 9 weeks (63 ±7 days) for subjects who discontinue trial treatment for reasons other than disease progression until the subject experiences confirmed disease progression or starts a new anti-cancer therapy.

Local reading (investigator assessment with site radiology reading) based on RECIST 1.1 will be used to determine subject eligibility and for subject management. Tumor imaging and assessment per local standard of care should be performed for patient management, and may include additional imaging (e.g. bone scan for prostate cancer patients) and appropriate tumor markers.

7.1.2.5.1 Initial Tumor Imaging

Initial tumor imaging must be performed within 28 days prior to the first dose of trial treatment. The site study team must review pre-trial images to confirm the subject has measurable disease per RECIST 1.1. The baseline imaging scan should be submitted to the central imaging vendor for a possible retrospective analysis of this eligibility criterion.

Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the first dose of trial treatment. The same imaging technique should be used in a subject throughout the study.

7.1.2.5.2 Tumor Imaging During Trial

Tumor imaging may be performed by CT or magnetic resonance imaging (MRI), but the same imaging technique should be used in a subject throughout the trial. Imaging should be performed every 9 weeks (63 days ± 7 days) from the first dose of trial treatment or more frequently if clinically indicated. Imaging should not be delayed for delays in cycle starts or withholding of pembrolizumab (MK-3475) cycle intervals.

Per RECIST 1.1, response should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date the response was first documented. The scan for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan, whichever is clinically indicated.

Imaging should continue to be performed until documented disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. Disease progression should be confirmed at least 4 weeks after the first scan indicating progressive disease in clinically stable subjects. Subjects who have unconfirmed disease progression may continue on treatment until progression is confirmed provided they have met the conditions detailed in Section 7.1.2.5.

7.1.2.6 Tumor Tissue Collection and Correlative Studies Blood Sampling

7.1.2.6.1 Tumor Tissue Collection

Mandatory tumor tissue (archival or newly obtained lesion) is required at screening. If archival tissue is not available, a newly obtained core or excisional biopsy of a tumor lesion will be obtained. The screening biopsy must be newly-obtained, which is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1. Tumor lesions not previously irradiated must be provided (tumors progressing in a prior site of radiation are allowed for PD-L1 characterization). PD-L1 characterization is not required prior to Cycle 1 Day 1. The PD-L1 characterization will be performed retrospectively.

Optional tumor tissue will be obtained pre- treatment (baseline), between C1D15 and C1D21, and at progression (if patient had complete response (CR), partial response (PR) or stable

disease (SD) > 27 weeks) provided there is technically biopsiable tumor, and it is safe for patient to undergo biopsy.

Core needle biopsies should be performed utilizing an 18 gauge needle or thicker whenever feasible or as directed by institutional standards. It is recommended that a minimum of 3 and up to 5 passes are required to ensure adequate tissue is obtained. Alternative biopsy procedures (e.g. cup, punch, excisional, incisional) that are expected to produce a tissue sample greater to or equal than a core biopsy with an 18 gauge core biopsies will also be acceptable. Four fine needle aspirates (FNAs) will also be obtained when feasible for additional exploratory molecular analysis (DNA, RNA, protein). The biopsy approach, number and size may be modified as needed based on tumor size and accessibility.

At screening, archived or newly obtained FFPE (formalin-fixed paraffin embedded) block or 20 unstained (5 micron) slides must be submitted for characterization at a central lab for PD-L1 characterization.

A fine needle aspirate, frozen sample, plastic embedded sample, cell block, clot, bone, bone marrow, cytologic specimen or formalin fixed samples frozen at any point will not be acceptable for IHC analysis. These samples will be sent to a central laboratory at Merck.

7.1.2.6.2 Correlative Studies Blood Sampling

Peripheral blood mononuclear cell (PBMC) will be collected as an optional procedure at baseline, tumor restaging, in conjunction with optional biopsies, and time of progression (if patients have had CR/PR/or SD for > 27 weeks). If patients do not elect to the optional biopsies, then the optional PBMCs will be collected at baseline, tumor restaging, and time of progression (if patients have had CR/PR/or SD for > 27 weeks). These samples will be sent to a central laboratory at Merck for the NanoString assay that will evaluate immune-related gene expression signatures and the potential to predict benefit from pembrolizumab.

7.1.2.7 Tumor Imaging for Correlative Studies

The correlative study imaging will incorporate the standard CT scan parameters or, in the case of MRI, the conventional MRI (T1 pre and post-contrast images, T2-weighted images (T2WI), Fluid attenuating inversion recovery (FLAIR) images) and other standard sequences routinely used. In the case of GBM tumors, additional advanced MRI (MR perfusion [dynamic susceptibility contrast (DSC), dynamic contrast enhancement (DCE) and arterial spin labeling (ASL)], MR- diffusion, and MR spectroscopy) sequences will be obtained. The CT or MRI tumor scans from tumor assessments at baseline, every 9 weeks (restaging), and at the end-of-treatment will be utilized for these correlative studies. Additional scans or time points will not be required. Imaging post-processing will include but not be limited to RECIST v1.1, advanced quantitative imaging and volume tumor metrics, and voxel-by-voxel radiome sequencing (texture, heterogeneity, energy, etc) imaging analysis.Image analyses will include non-invasive assessments of cell death (apoptosis), active tumor proliferation, tumor invasion, tumor density, vascularity, vascular permeability, microvascular density and metabolite

profiles. Exploratory analyses will utilize quantitative imaging tumor metrics and radiome sequencing for texture maps to assess gene signatures of tumor cell apoptosis, invasion and immune cell infiltration. Exploratory analysis using quantitative imaging tumor metrics and texture maps will also be used to assess pseudoprogression, progression and response. These analyses will be compared to a retrospective cohort of patients that have been dichotomously analyzed for lack of inflammatory response versus robust intratumoral inflammatory responses to prospectively validate the sensitivity and specificity of this approach.

7.1.2.8 Serial Mutation Assessment

Patients enrolled on this study will be approached for co-enrollment on PA11-0852 Clearinghouse protocol for germline testing for the MD Anderson Cancer Center Personalized Cancer Therapy Program. We expect most patients enrolled will have had hot spot mutation testing or targeted exome profiling performed through the Clearinghouse protocol. If evidence of clinical activity is seen, targeted exome sequencing on a 200-400 gene platform or larger will be performed in patients with objective responses and prolonged stable disease > 27 weeks as well as any patients with rapid progression (this would be done as part of a Institute of Personalized Cancer Therapy Unusual Responder Program. In addition patients who have a mixed response of response with subsequent progression will be approached for optional biopsies for molecular characterization as well as generation of patient-derived xenografts and conditionally-reprogrammed cells. This evaluation will determine the evolution of the mutation and will facilitate functional characterization. Plasma mutations may be assessed with digital PCR or next generation sequencing.

As per the PA11-0852 Clearinghouse protocol, the optional tumor biopsies from baseline and the time of progression (if progression after response or unexpected rapid progression) will be analyzed. Development of new mutations or reversal of the mutations will be analyzed and correlated with clinical response. This will be our exploratory objective and no formal statistical analysis will be done.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 7.

Table 7 Laboratory Tests

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

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

‡ If considered standard of care in your region.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 28 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours (3 days) prior to each dosing on Day 1 of each subsequent cycle. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.5. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

7.1.4.2 Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

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 Period

Approximately 28 days prior to enrollment, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

After providing main study consent, subjects will undergo the screening period. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of trial treatment except for the following:

- Laboratory tests are to be performed within 28 days prior to the first dose of trial treatment
- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours (3 days) prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory)
- Archival tissue collection for PD-L1 characterization are not required to be completed

within 28 days prior to the first dose of trial treatment

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

7.1.5.2 Treatment Period

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

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 (± 7 days) after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab (as described in Section 7.1.5.5) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

7.1.5.4 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 9 weeks (63 ± 7 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section 7.1.5.5. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 7.1.5.5 will move from the follow-up phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.1 – Trial Flow Chart for Retreatment.

7.1.5.4.1 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone

every 12 weeks (± 4 weeks) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.5.5 Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab with SD or better may be eligible for up to one year of additional pembrolizumab therapy if they progress 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 27 weeks (9 cycles) with pembrolizumab before discontinuing therapy
    - Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

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

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 5.1.2
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.

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

- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

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 and Recording Adverse Events

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

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

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

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

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

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

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

The study drug-related adverse event data will be collected and stored in the Investigational Cancer Therapeutics database, Molecular and Clinical Data Integrated Platform (MOCLIP). The PI or designee will be responsible for determining attribution for all events, and this will be documented in the electronic medical record.

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the IND 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 IND Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

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

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the

completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

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

7.2.3.1 Serious Adverse Events

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

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

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

- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.**
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- **Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.**
- **Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**
- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.**

Reporting to FDA:

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

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

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

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

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

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

7.2.3.2 Events of Clinical Interest

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

For the time period beginning when the consent form is signed until treatment, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the IND 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 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 IND Sponsor and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

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

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

> *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section 7.2.3.- Immediate Reporting of Adverse Events to the IND Sponsor and to Merck, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the IND Sponsor within 24 hours and to Merck Global Safety within 2 working days either by electronic or paper media.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The IND Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Merck Global Safety as a SAE

within 2 working days of determination that the event is not progression of the cancer under study

Hospitalization related to convenience (e.g.transportation issues etc.) will not be considered a SAE.

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 4.03. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

Table 8 Evaluating Adverse Events

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

V4.03 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Merck product to be discontinued?	
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9).

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. There will be 10 cohorts included in the overall population of different cancer types. All patients who have received at least 3 doses of study medication will be included in both the safety and efficacy analyses. If a patient has not received 3 doses of study drug, they will be considered inevaluable and will not be included in the efficacy analysis. However the patient will be considered for the toxicity analysis. In particular if a patient withdraws early due to toxicity, the patient will be included in the toxicity analysis

8.1.1 General Analyses

Tabulations will be produced for appropriate demographic, baseline, efficacy and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented, as well as two-sided 95% confidence intervals, unless otherwise stated. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals, as well as percentage of censored observations.

8.1.2 Efficacy Analyses

Clinical efficacy will be measured by non-progression rate (NPR) at 27 weeks as defined as the percentage of patients who are alive and progression-free at 27 weeks as assessed RECIST criteria. A 95% confidence interval of response rate will be estimated based on a binomial distribution.

8.1.3 Safety Analysis

For the objective of describing the toxicity profile, descriptive statistics will be provided on

the grade and type of toxicity by dose level.

8.1.3.1 Adverse Events

Adverse Events (AEs) will be coded using the NCI-CTCAE (4.03) dictionary and displayed for all study patients combined. Analyses of AEs will be performed for those events that are considered treatment emergent, where treatment-emergent is defined as any AE with onset or worsening of a pre-existing condition on or after the first administration of study medication through 30 days following last dose or any event considered drug-related by the investigator through the end of the study. AEs with partial dates will be assessed using the available date information to determine if treatment-emergent; AEs with completely missing dates will be assumed to be treatment-emergent.

AEs will be summarized by patient incidence rates, therefore, in any tabulation, a patient contributes only once to the count for a given AE preferred term. The number and percentage of patients with any treatment-emergent AE will be summarized for all study patients combined. The number and percentage of patients with treatment-emergent AEs assessed by the Investigator as at least possibly related to treatment will also be tabulated. The number and percentage of patients with any grade ≥ 3 treatment-emergent AE will be tabulated in the same manner. In the event a patient experiences repeated episodes of the same AE, then the event with the highest severity and/or strongest causal relationship to study treatment will be used for purposes of tabulations. Serious AEs will also be tabulated.

No formal hypothesis-testing analysis of AE incidence rates will be performed. All AEs (treatment emergent and post-treatment) will be listed in patient data listings. By-patient listings will be provided for the following: patient deaths; serious AEs; and AEs leading to withdrawal.

8.1.3.2 Laboratory Data

The actual value and change from baseline to each on study evaluation will be summarized for each clinical laboratory parameter, including hematology and clinical chemistry, for all study patients combined. In the event of repeat values, the last non-missing value per study day/time will be used. Severity of select clinical lab measures will be determined using CTCAE criteria (e.g. those measures that have a corresponding CTCAE grade classification). Labs with CTCAE grades greater than or equal to 3 will be presented in a data listing. Shift tables that present changes from baseline to worst on-study values relative to CTCAE classification ranges will be produced.

8.1.4 Power and Sample Size

The sample size for this study is based on the Simon's optimal two-stage design.[17]

This trial has futility interim analyses for 10 well-defined expansion cohorts and the endpoint is 27-week PFS (referred to as non-progression rate, NPR). Each cohort will follow a two-stage design with 12 patients in the first stage and 13 in the second stage. If among the 12

patients enrolled in the first stage, 3 or more patients are alive and progression-free at 27 weeks, enrollment into the second stage will begin. If more than 7 of the 25 total patients in a cohort are alive and progression-free at 27 weeks, the drug will be considered worthy of further study in that cohort. The null success rate is set at 20% and the alternative at 40% for each cohort. This design has a 10% Type I error rate, 82% power and 56% probability of stopping after the first stage if the true 27-week PFS rate is 20%.

The maximum accrual will be 250 patients (25 patients x 10 cohorts). In order to get 250 evaluable patients, up to 275 patients may need to be enrolled.

8.1.5 Interim Analyses

In accordance with the Simon two-stage study design described in Section 8.1.4, there will be a preliminary assessment of efficacy for each cohort after the first 12 patients enrolled in that cohort have 27-week data available to assess efficacy. Note that this initial analysis for a cohort may take place sooner than when the 12th patient has available data, should there be 3 or more responders after fewer than 12 patients are enrolled. Should the trial be terminated at the first stage, all efficacy and safety analyses as noted above will be performed. Patient enrollment will be suspended pending observation of the needed numbers of responses.

Response Monitoring:

- STAGE 1:
  A Futility Summary will be submitted to the IND Medical Monitor after 12 subjects are evaluable for response (at 27 weeks) per cohort.

- STAGE 2:
  A final Response Summary will be submitted to the IND Medical Monitor after there are 25 evaluable patients for response per cohort.

The final analysis for each cohort will take place after there are 25 patients evaluable for analysis of efficacy. Additional data summarization may take place after all available survival data are collected, or after investigator decision, as appropriate.

8.2 Statistical Analysis Plan

8.2.1 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be the responsibility of the University of Texas MD Anderson Cancer Center, Biostatistics department. A detailed analysis plan has been developed and will be implemented.

8.3 Study Objectives

8.3.1 Primary Objective

Objective: To obtain early indication of efficacy by evaluation of non-progression rate (NPR) at 27 weeks as defined as the percentage of patients who are alive and progression-free at 27 weeks, as assessed by RECIST in patients with advanced tumor types receiving pembrolizumab.

8.3.2 Secondary Objectives

(1) **Objective**: To correlate efficacy by evaluation of tumor size to PD-L1 status among patients with advanced tumor types receiving pembrolizumab.

(2) **Objective:** To evaluate safety and tolerability of pembrolizumab in patients with advanced tumors.

(3) **Objective:** To evaluate the percentage of patients with objective response (CR or PR), progression free survival (PFS), overall survival (OS), and duration of response (DOR) in patients with advanced tumor types receiving pembrolizumab.

(4) **Objective:** To evaluate the NPR at 27 weeks (9 cycles) and objective response (CR or PR) as assessed by irRECIST in patients with advanced tumor types receiving pembrolizumab.

(5) **Objective:** To correlate the NPR at 27 weeks (9 cycles), objective response (CR or PR), PFS, OS, and DOR to PD-L1 status among patients with advanced tumor types receiving pembrolizumab.

8.3.3 Exploratory Objectives:

(1) **Objective:** To evaluate the potential role of tumor-associated immune biomarkers for prediction of therapy effectiveness in patients with advanced tumor types receiving pembrolizumab.

(2) **Objective:** To correlate the potential role of tumor-associated immune biomarkers for prediction of therapy effectiveness to PD-L1 status among patients with advanced tumor types receiving pembrolizumab.

(3) **Objective:** To identify imaging characteristics associated with immunological changes in tumor following treatment with pembrolizumab.

(4) **Objective:** To compare tumor mutation burden and serial assessment of mutation status in biopsies obtained at baseline and progression in patients with advanced tumor types receiving pembrolizumab.

8.4 Hypotheses:

Intravenous administration of single agent pembrolizumab (MK-3475) to subjects with a given PD-L1 positive advanced tumor type will result in an NPR at 27 weeks greater than 20% based on RECIST 1.1 criteria.

8.5 Analysis Endpoints

Efficacy endpoints will be evaluated as aggregate and between PD-L1 and non-PD-L1 expressing tumor types within and across tumor types.

8.5.1.1 Efficacy Endpoints

The primary efficacy endpoint is NPR at 27 weeks, defined as the proportion of subjects in the analysis population who have has no progression of disease by 27 weeks. Response for the primary analysis will be determined by the investigator assessment, and a confirmation assessment is required per RECIST 1.1.

Secondary efficacy endpoints include: (1) objective response, CR, PR or SD according to RECIST, v1.1; (2) duration of response, defined as time from first RECIST 1.1 response to disease progression in subjects who achieve a PR or better; (3) progression-free survival (PFS), defined as the time from allocation to the first documented disease progression according to RECIST 1.1 or death due to any cause, whichever occurs first; and (4) overall survival (OS); (5) NPR and objective response (CR or PR) according to irRECIST.

Additional supportive analyses of best overall response rate, duration of response, and PFS will be conducted by using modified RECIST 1.1 criteria, in which a confirmation assessment of disease progression must be obtained at least 4 weeks after the initial disease assessment indicating progressive disease. Response for the secondary analysis will be determined by irRECIST.

8.5.1.2 Safety Endpoints

The primary safety endpoints are AEs graded using CTCAE (Version 4.03) criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab (MK-3475), including serious adverse events (SAEs), events of clinical interest (ECIs), and immune-related adverse experiences (irAEs). Other safety endpoints include laboratory safety assessments, ECOG performance status, vital signs and physical examinations.

8.5.1.3 Exploratory Endpoints

Image analyses will include non-invasive assessments of cell death (apoptosis), active tumor proliferation, tumor invasion, tumor density, vascularity, vascular permeability, microvascular density and metabolite profiles. Exploratory analyses will utilize quantitative imaging tumor metrics and radiome sequencing for texture maps to assess gene signatures of tumor cell

apoptosis, invasion and immune cell infiltration. Exploratory analysis using quantitative imaging tumor metrics and texture maps will also be used to assess pseudoprogression, progression and response. These analyses will be compared to a retrospective cohort of patients that have been dichotomously analyzed for lack of inflammatory response versus robust intratumoral inflammatory responses to prospectively validate the sensitivity and specificity of this approach.

8.5.2 Analysis Populations

The population analysis will be evaluated as aggregate data, by tumor indication, and between PD-L1 and non-PD-L1 expressing tumor types.

8.5.2.1 Efficacy Analysis Populations

There will be 10 cohorts included in the overall population of different cancer types. The safety population will be the main population for all analyses (demographics, efficacy and safety) unless otherwise stated. The modified intent-to-treat (ITT) population will include all patients enrolled in the study that received at least three doses of drug.

8.5.3 Statistical Methods

Tabulations will be produced for appropriate demographic, baseline, efficacy and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter will be presented, as well as two-sided 95% confidence intervals, unless otherwise stated. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values will be presented. Time-to-event data will be summarized using Kaplan-Meier methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals, as well as percentage of censored observations.

No imputation of missing efficacy data is planned. For time to event analyses, patients who have no efficacy evaluations for disease recurrence will be considered censored at time 0.
For adverse events (AEs), missing dates will not be imputed, however, if partial dates are available, they will be used to assess if the AE occurred during the treatment period. Missing severities of AEs will not be imputed and will be considered missing in any tabulations of AE severity. If an AE is missing a response to the question regarding relationship to treatment, the event will be considered to be related.

No adjustments for multiple testing will be performed. All inferences beyond those involved in the Simon design will be considered exploratory. Unless otherwise stated, all statistical tests will be conducted at the α=0.05 (2-sided) level.

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 9.

Table 9 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 IND 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 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

1. Name, address, telephone number and e-mail address;
2. Hospital or clinic address and telephone number;

3. Curriculum vitae or other summary of qualifications and credentials; and
4. Other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the IND Sponsor, and subsidiaries, affiliates and agents of the Merck, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the IND Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

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

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory

authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

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

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

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

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

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

The investigator will promptly inform the IND Sponsor of any regulatory authority

inspection conducted for this trial.

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

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

According to European legislation, a IND Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the IND Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the IND Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The IND Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

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

10.5 Quality Management System

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

10.6 Data Management

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

This study will be monitored by the University of Texas MD Anderson IND Office, and a protocol-specific monitoring plan will be followed.

All patients who meet eligibility criteria and are enrolled in this trial will be registered in Clinical Oncology Research Database (CORe) at the University of Texas MD Anderson Cancer Center at Houston. Data will be collected and stored in the Investigational Cancer Therapeutics database, Molecular and Clinical Data Integrated Platform (MOCLIP).

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 V4.03 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 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.

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